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VOLUME 10, NUMBER 7

## GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*WALTER C. ALVAREZ, *Editor*A. C. IVY, *Assistant Editor*

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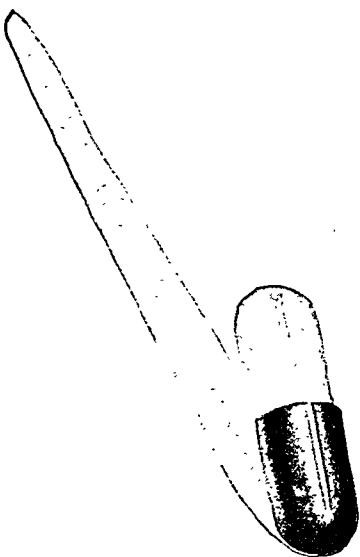
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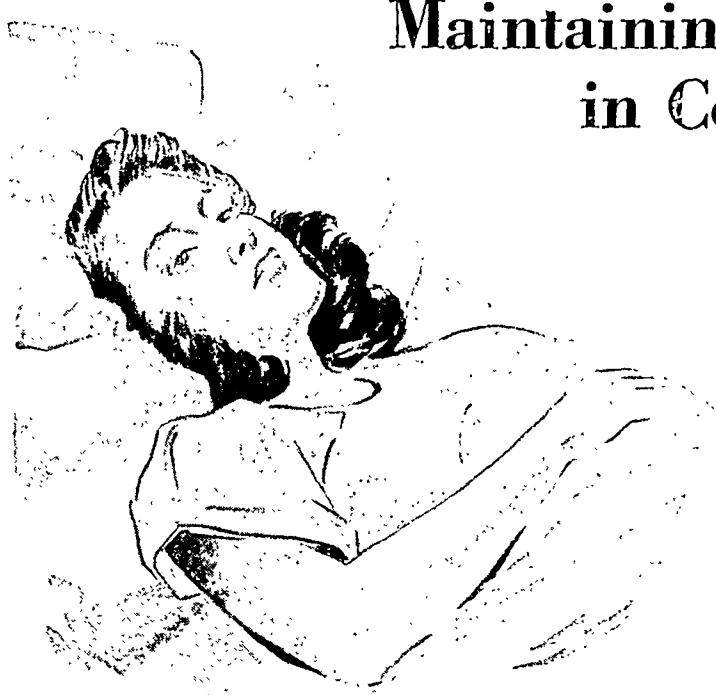
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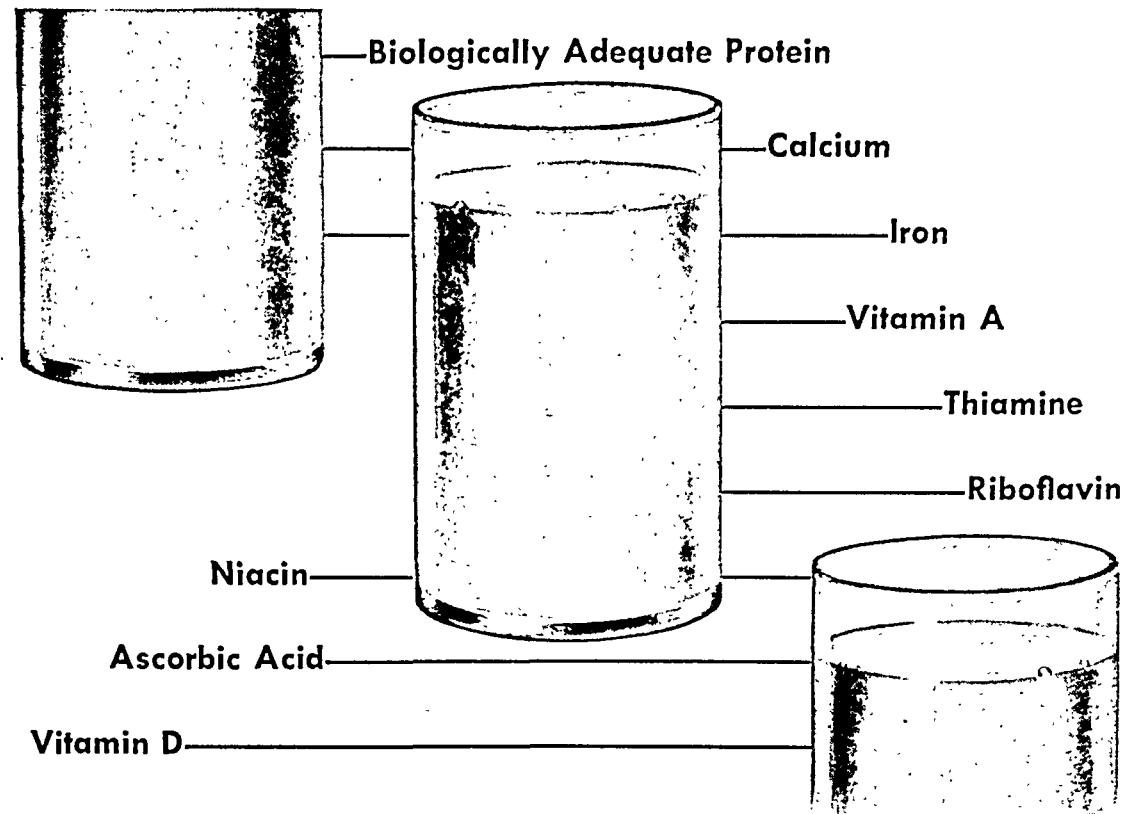
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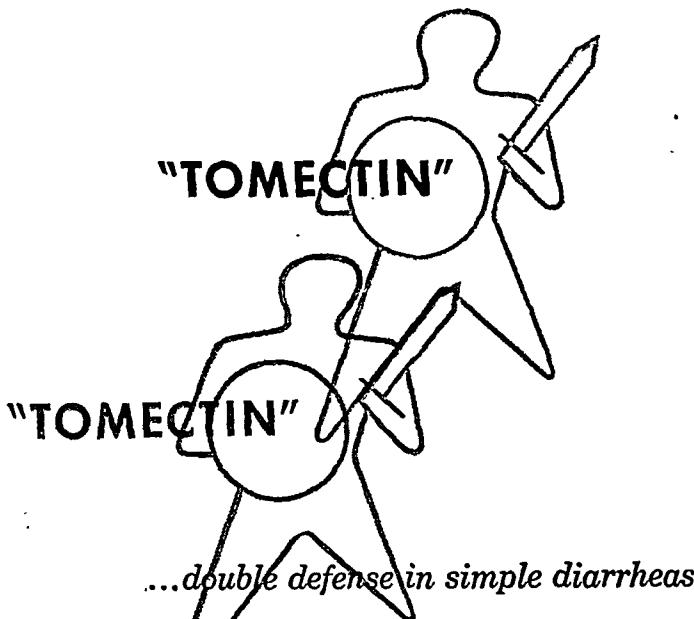


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<sup>1</sup>Block, L. H., Tarnowski, A., and Green, B. L.

Am. J. Digest. Dis. 6:96 (Apr.) 1939

<sup>2</sup>Morrison, L. M.: Am. J. Digest. Dis. 13:196 (June) 1946



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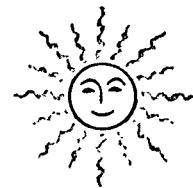
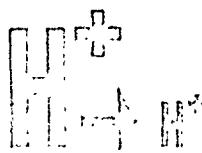
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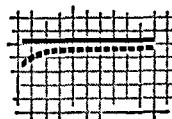
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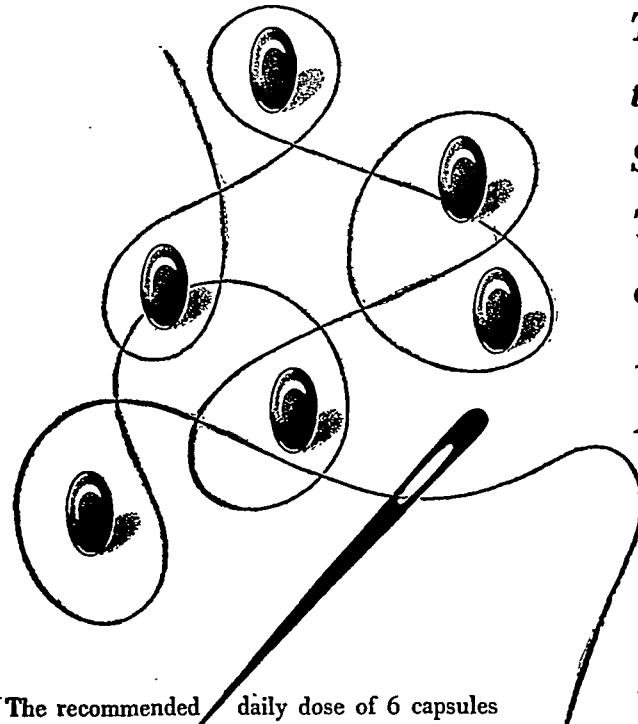
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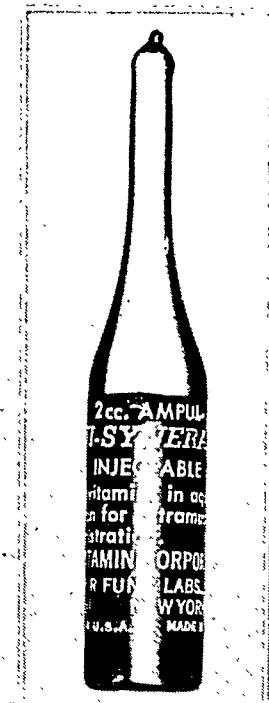
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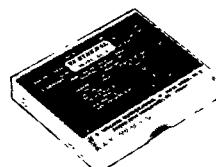
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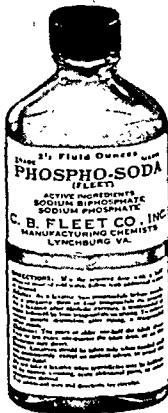
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References: 1. Gold, Harry: In Conferences on Therapy, N. Y. State J. of Med., Mar. 1, 1947. 2. Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics, The Macmillan Co., New York, 1941. 3. Osol, A. and Farrar, G. E.: Dispensatory of U.S.A., J. B. Lippincott Co., Philadelphia, 24th ed., 1947. 4. Sollmann, T.: A Manual of Pharmacology, W. B. Saunders Co., Philadelphia, 7th ed., 1948. 5. Loc. cit., p. 750.

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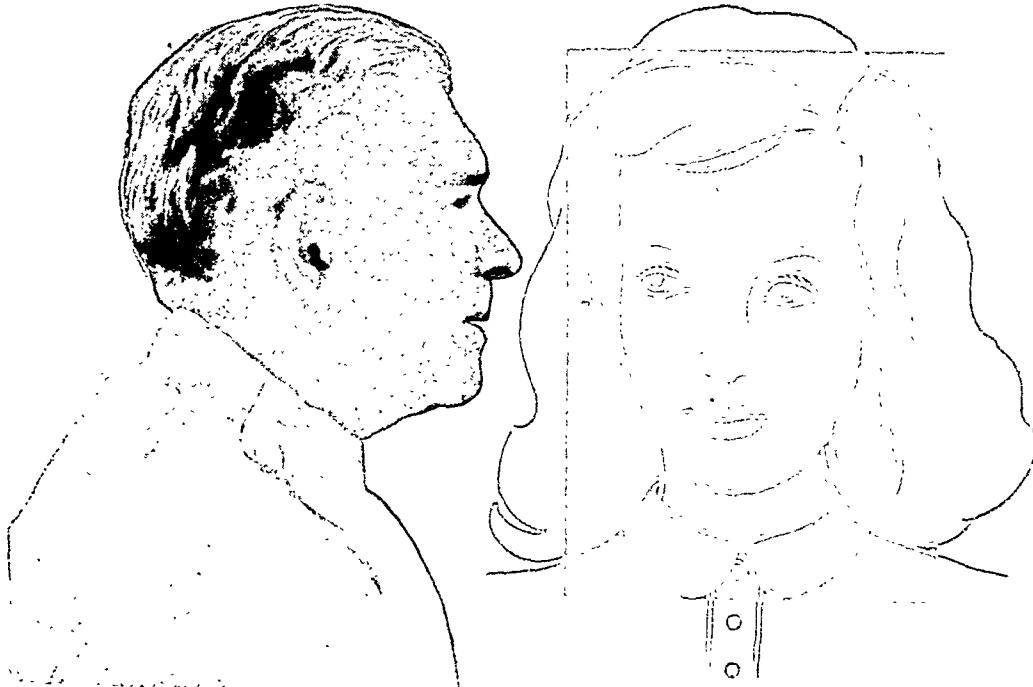


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# GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*

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VOLUME 11

July 1948

NUMBER 1

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## CHRONIC RELAPSING PANCRÈATITIS: AN ANALYSIS OF 27 CASES ASSOCIATED WITH DISEASE OF THE BILIARY TRACT

EARL E. GAMBILL, M.D., AND MANDRED W. COMFORT, M.D.

*Division of Medicine*

AND

ARCHIE H. BAGGENSTOSS, M.D.

*Division of Pathologic Anatomy*  
Mayo Clinic, Rochester, Minnesota

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### INTRODUCTION

Chronic relapsing pancreatitis typically manifests itself by recurring attacks of pain usually in the upper part of the abdomen, by disturbances of function of acinar and islet cells, and by certain sequelae. It is a distinct clinical entity which does not require the presence of disease of the biliary or gastro-intestinal tract for its inception or continuation. However, in many cases, disease of the biliary tract also is present. In such cases, certain pertinent questions may be asked. When cholelithiasis is present does it alter the clinical picture, the laboratory findings and the course of pancreatitis from what we found them to be in 29 cases of pancreatitis unassociated with disease of the biliary tract?<sup>1</sup> Are the pathologic alterations of the pancreas different when cholelithiasis is present? In what way are the problems of diagnosis, treatment and prognosis altered by the coexistence of disease of the biliary tract? In short, is chronic relapsing pancreatitis the same or a different disease when disease of the biliary tract is present? Finally, is the acute seizure of pancreatic disease secondary to disease of the biliary tract as is commonly assumed, or is the disease of the biliary tract secondary to the pancreatic disease or does the disease in the two organs appear simultaneously?

In the following pages we shall present an analysis of the 27 cases of chronic relapsing pancreatitis associated with disease of the biliary tract that were encountered in the years 1939 through 1943 and shall compare this with an analysis of the 29 cases of chronic relapsing pancreatitis without disease of the biliary tract that were encountered during the same years.<sup>1</sup> We shall point out the similarities and the dissimilarities in the analyses of the two series in the hope that we can answer, partly at least, some of the above-stated questions.

In each of the 27 cases herein analyzed, disease of the biliary tract had been or was present, a history of recurring painful abdominal seizures was obtained and the existence of pancreatitis was proved by surgical exploration, biopsy or necropsy.

#### TYPICAL ILLUSTRATIVE CASES

As in the analysis of the 29 cases of chronic relapsing pancreatitis without associated disease of the biliary or gastro-intestinal tract, the cases in the present series are grouped readily in respect to the presence of painful seizures alone, or together with 1, 2 or all 3 of those diagnostically important sequelae of chronic relapsing pancreatitis; namely, calcification, steatorrhea and diabetes.

In 19 of the 27 cases, repeated exacerbations of the disease, as indicated by painful seizures, had not been followed by calcification, steatorrhea or diabetes at the time of examination. Cases 1 and 2 are illustrative examples.

*Case 1.*—A man aged 37 years registered at the clinic February 1, 1939. The first of a series of attacks of upper abdominal pain was experienced in 1928 at the age of 26. In the interval between 1928 and 1939 approximately 50 attacks had occurred. The early attacks lasted as long as two to four days and the pain and tenderness were located in the right upper quadrant of the abdomen. The episodes were severe, requiring morphine for relief, and were usually accompanied by nausea and vomiting but not by chills or fever. Later, the distress extended to the back and the pain and tenderness spread to the left upper part of the abdomen. The residual tenderness commonly persisted for three to four days.

In May, 1931, appendectomy and cholecystostomy were performed. Stones were not found. The pathologic description of the gallbladder was not available but the gallbladder was said to be diseased. The attacks continuing, exploration of the abdomen for intestinal obstruction was done in November, 1931; adhesions were cut. The attacks recurring with increasing frequency, a postoperative ventral hernia was repaired in 1934. Adhesions prevented removal of the gallbladder. The attacks recurred, became increasingly severe, often requiring for relief several hypodermic injections of morphine in doses of  $\frac{1}{2}$  grain (32 mg.), and were followed by persistent vomiting for as long as a week. The vomitus occasionally was of the retention type.

The patient arrived at the clinic in the interval between attacks. General physical examination gave essentially negative results. Urinalysis, blood counts and routine serologic test for syphilis gave normal or negative results. On February 2, roentgenograms of the gallbladder after administration of dye revealed a functioning organ without stones. In the roentgenograms of the region of the kidneys, ureters and bladder, small areas of calcification were noted in the vicinity of the liver and spleen. Roentgenoscopic examination of the stomach and duodenum disclosed that the duodenum was deformed by fixation in the region of the gallbladder.

On February 9, a painful seizure started. The concentration of bilirubin in the blood serum was 1.7 mg. per 100 cc., the van den Bergh reaction was indirect and the bromsulfalein test of hepatic function did not disclose retention of dye. The diagnosis was stone in the common duct.

Surgical exploration was carried out February 13, 1939. It was noted that the head of the pancreas was enlarged and hard, that the common bile duct was 2 cm. in diameter, that the gallbladder was thick-walled, edematous and subacutely inflamed, that diffuse mesenteric lymphadenitis was present and that the liver was the seat of a hepatitis (brownish in color) and contained multiple small fibrous calcified nodules measuring 1 to 2 mm. in diameter. The common bile duct was opened and explored; no stones were found. A large-sized scoop passed through the lower end of the common bile duct into the duodenum without encountering resistance. A T tube was left in the common bile duct. Cholecystectomy was performed. The surgical diagnosis was subacute cholecystitis without cholelithiasis, hepatitis grade 4, pancreatitis grade 4 (both on the basis of 1 to 4, in which 1 represents the least, and 4 the most severe condition), mesenteric lymphadenitis and healed peritoneal tuberculosis.

The pathologist reported subacute cholecystitis superimposed on chronic cholecystitis, with infiltrated and edematous walls. The lymph nodes were the site of inflammation. The nodules from the liver were fibrous, calcified and probably represented healed tuberculosis. A culture of bile from the common bile duct did not reveal a growth of organisms.

Choledochograms on March 1 and April 10 outlined the hepatic ducts and showed the medium entering the duodenum freely. Filling defects indicative of stone were not noted. On April 11 and 13 acute attacks of abdominal pain occurred. After removal of the T tube about May 20, severe attacks of pain recurred May 27, August 13, August 27, September 18, September 25 and October 22. The pain was located in the right upper quadrant and extended to the right scapular area. The pain lasted ten to twelve hours and required hypodermic injections about five or six hours apart,  $\frac{1}{2}$  grain (32 mg.) of morphine being given at the onset and  $\frac{1}{4}$  grain (16 mg.) at intervals thereafter. The attack was associated with nausea and vomiting and residual soreness. The pain had not spread to the left upper quadrant. Each attack was followed by jaundice.

On November 6, 1939, physical examination gave negative results. Urinalysis, blood counts and routine serologic test for syphilis gave negative or normal results. The concentration of bilirubin was 1.3 mg. per 100 cc. and the van den Bergh reaction was indirect. The bromsulfalein test of hepatic function did not show retention of dye. The activity of amylase in the serum was normal but that of lipase was slightly elevated. The secretin test of external pancreatic secretion disclosed a definite diminution in pancreatic secretory function.

On January 22, 1946, his physician wrote that the patient still was having occasional attacks of pain such as he was having at the time of his last visit to the clinic but that the attacks were considerably further apart and much less severe. An injection of morphine occasionally was necessary.

*Case 2.*—A 40 year old female registered at the clinic March 28, 1940. The family history was not significant. The patient complained of recurrent attacks of abdominal pain, with chills, fever and jaundice. The first attack occurred in 1926, two days post partum. The pain was situated in the right upper quadrant of the abdomen, was not colicky, was steady and extended to the right scapula. There were nausea, vomiting, fever and jaundice but no chills. The attacks varied from three hours to three days in duration and required morphine for relief. Between attacks there were bloating and belching. The attacks occurred about three to four times yearly until 1933, when they became more frequent, occurring as often as once weekly.

In April, 1934, cholecystectomy and choledochostomy were performed for chronic cholecystitis associated with stones in the gallbladder and common duct. A T tube was inserted but removed after seven days. In September, 1936, the attacks recurred. Twelve attacks occurred from September to December, 1936, when exploration again was carried out. A stricture was found at the ampulla. This was dilated. A T tube was inserted and allowed to remain for fourteen days. Pancreatitis was noted. The patient again was free from symptoms until August, 1939, when these attacks recurred. They rapidly increased in frequency so that they were occurring every one or two days at the time of registration. The attacks of pain remained midepigastric and right upper quadrant in location and were still associated with nausea, vomiting and fever, as they were before cholecystectomy. Abdominal distention accompanied the attacks. The occurrence of borborygmi signalled the end of the attack. The patient's digestion was constantly upset and she lost weight and strength.

On physical examination the systolic blood pressure was 92 and diastolic 60, expressed in millimeters of mercury. The edge of the liver was rounded, firm and nontender and was felt about a finger's breadth below the right costal margin. There was some tenderness in the epigastrium. Urinalysis gave negative results. The hemoglobin measured 13.2 gm., erythrocytes numbered 4,480,000 and leukocytes 9,600 per cu.mm. of blood. The results of routine serologic tests for syphilis and roentgenographic examination of the chest were negative. The concentration of bilirubin in the serum was 1.9 mg. and the van den Bergh reaction was direct. The activity of amylase was 160 units and that of lipase 4.0 cc. of twentieth-normal sodium hydroxide per cubic centimeter of serum. The patient was afebrile. On April 8, the activity of amylase was 160 units and that of lipase 1.1 cc. Excretory urograms did not disclose abnormalities of the upper part of the urinary tract. The diagnosis was stone in the common duct, with secondary pancreatitis.

On April 3, 1940, exploration was carried out. The liver was dusky in color but its surface was smooth. The stomach and duodenum were plastered to the hilus of the liver. The common duct was approximately 2.5 cm. in diameter and its walls were markedly thickened. There was a firm mass in the head of the pancreas. The common bile duct was opened, normal-looking bile was obtained, no stones were encountered and there was pronounced dilatation of the intrahepatic ducts. Scoops slipped into the duodenum without difficulty. Choledochoduodenostomy

was done. The surgical diagnosis was chronic pancreatitis, grade 3, and hepatitis, grade 2. The postoperative course was uneventful. On April 8, the activity of amylase was 160 units and that of lipase 1.1 cc. On April 16, the glucose tolerance test gave a normal curve. The patient was dismissed on April 22.

The patient last was seen October 31, 1940. She had had no further symptoms and had gained 35 pounds (15.9 kg.) and much strength. There had been no pain or dyspepsia. The bowels moved regularly. The fasting concentration of sugar in the blood was 95 mg. per 100 cc., the activity of lipase was 0.9 cc. of twentieth-normal sodium hydroxide per 1 cc. of serum, and the value for serum amylase was 100 units. A letter dated August 10, 1945, stated that she had had no further pain or dyspepsia.

*Comment.*—Cases 1 and 2 are typical of the 19 cases of this series in which the pancreatitis revealed itself by painful seizures occurring over a period of years without the appearance of calcification, steatorrhea or diabetes. In both cases the painful seizures were severe, frequent, tended to last days, not hours, and in case 1 to spread to or involve the left side of the body, features which we shall point out as suggestive of pancreatitis no matter whether cholelithiasis is or is not associated.

In case 1, as in 10 other cases of the series, stones were not present either in the gallbladder or common bile duct. In case 2, stones had been removed from both the gallbladder and common bile duct. Stones had been or were present in 15 other cases of the series but only in case 2 were stones present in the common duct. Thus, cases 1 and 2 illustrate that calculous disease may or may not accompany the cholecystitis of this series.

Two features of case 1 are especially interesting. First, in the intervals between attacks the cholecystitis was not of a degree great enough to interfere with the function of the gallbladder measured by cholecystogram and yet the painful seizures had been frequent and severe over a period of eleven years. It seems unreasonable to explain attacks of such severity and number on the basis of such a degree of noncalculous cholecystitis, and under such a combination of findings cholecystitis should not be accepted as the cause of the painful seizures; a search for other causes should be made. Second, the gallbladder, functioning normally in the interval between attacks, was found during an acute seizure to be the seat of severe cholecystitis. It was described by the surgeon and pathologist as a subacute or a chronic cholecystitis associated with infiltrated, thickened and edematous walls. It seems likely that similar acute episodes of cholecystitis in the past had subsided leaving little residual damage in the intervals, as we have good reason to believe occurred in case 13 of the previously reported series of cases of chronic pancreatitis without cholelithiasis.<sup>1</sup> The question is well worth asking, Did the acute process originate in the gallbladder or the pancreas or simultaneously in both? Customarily, the accusing finger has been pointed at the gallbladder as the primary offender,

the pancreas as the long-suffering innocent bystander, but in cases like this such an interpretation has little justification and appears to be only a relic of the days when the pancreas was considered the seldom diseased, silent organ of the body. Certainly in case 1, pancreatitis better explains the symptomatology than does cholecystitis. On the contrary, in case 2 the coexistence of chronic cholecystitis with the pancreatitis may not be questioned; case 2 is the type which encourages the assumption that disease of the biliary tract precedes, and is responsible for, the pancreatitis.

In 8 of the 27 cases, one or more of the diagnostically important sequelae of diabetes, steatorrhea and deposition of calcium in the pancreatic parenchyma or in the pancreatic ducts had appeared when the patient was examined. Thus, diabetes had developed in 1 case, gross steatorrhea in 1, calcification in 3, calcification and diabetes in 1, calcification and gross steatorrhea in 1 and calcification, diabetes and steatorrhea in 1. The following case illustrates these features of pancreatitis.

*Case 3.*—A 46 year old restaurant and tavern worker first came to the clinic July 6, 1942, complaining of attacks of abdominal pain for the past ten years. He had used alcohol heavily until the onset of his trouble. His physician stated that the attacks seemed to follow alcoholic indiscretion. For ten years he had suffered from recurring attacks of severe pain in the midepigastrium and right upper quadrant, which extended through to the middle part of the back and required hypodermic injections for relief. The attacks would last several days to two weeks. Originally they occurred two or three times a year and later increased to three or four times a year. On November 26, 1941, cholecystectomy was performed. Stones were found in the gallbladder and cystic duct. Since that date the same type of attacks had continued to occur and were associated at times with jaundice. In April, 1942, the patient had undergone an exploratory laparotomy, at which time a large, hard, nodular pancreas was noted. In the interval between that operation and his admission to the clinic he suffered constant, daily midepigastric aching pain that required hypodermic injections one to three times a day. He had lost considerable strength and 70 pounds (31.8 kg.) and was costive. He had had general malaise and a poor appetite.

Physical examination disclosed normal blood pressure, pulse and temperature. A hard, tender, multinodular and slightly movable mass was felt in the epigastrium. Routine urine and blood studies gave essentially normal results. A differential count of the blood revealed 10.5 per cent eosinophils. The serum amylase and lipase were normal on five different occasions. The sedimentation rate varied from 45 to 63 mm. in one hour by the Westergren method. The bromsulfalein test of hepatic function revealed no retention of dye. The concentration of bilirubin in the serum and the values for fasting blood sugar and blood fats were normal. The results of roentgenologic examination of the stomach and duodenum were negative. Roentgenograms of the pancreatic region showed multiple pancreatic calculi. Examina-

tion of the stool revealed that 34.5 per cent of the fecal solids were fat. The glucose tolerance test (standard) gave a diabetic type of curve.

Surgical exploration on July 13, 1942, revealed a normal stomach and duodenum. The head of the pancreas was the size of a man's fist and quite firm, tapering off toward the tail. The common bile duct was about one and a half times normal size; its walls were thickened, but no stones were found. Scoops and probes could not be passed into the duodenum, the lower end of the common duct being completely surrounded by the pancreas. The liver seemed normal. Choledochoduodenostomy was performed. No bacteria were found on culture of bile from the common duct.

The patient returned November 21, 1942, stating that the old attacks of pain had recurred two weeks previously. The attacks were midepigastric in location, extending both to the right and to the left costovertebral regions, and were severe enough to require use of opiates. The results of urinalyses were negative; the glucose tolerance test revealed the concentrations of blood sugar before, a half hour after, two hours after and three hours after administration of 100 gm. of glucose to be, respectively, 125, 158, 250 and 146 mg. per 100 cc. The specimens of urine collected before the test and a half hour after administration of glucose did not contain sugar but those collected two hours and three hours after administration of glucose contained, respectively, 0.816 gm. and a slight amount of glucose. The patient was having one or two stools daily and fat represented 34.5 per cent of the dried weight of the feces. Analysis of external pancreatic secretion after stimulation with secretin revealed low values for enzymes. Deep roentgen therapy over the pancreas was given.

The patient last was seen in June, 1946. He stated that he had had recurring attacks of pancreatic pain at frequent intervals during 1943, that he had had no such attacks in 1944 but that three had occurred in 1945 and one so far in 1946. The attacks were midepigastric and extended to the left costovertebral angle. The duration of severe pain was one or two days but a mild pain persisted three or four weeks in the costovertebral angle after each attack. Nausea, vomiting, chills and fever were features of the painful seizures. Between attacks one and sometimes two bulky light-colored stools usually appeared after each meal. He had noted droplets of oil floating on the water of the toilet. The excessive use of alcohol definitely precipitated the attacks, and fat in excess in the diet increased the number of stools. After each attack the number of stools increased to ten or twelve daily.

The results of urinalysis, the value for hemoglobin, the number of erythrocytes and the concentrations of fasting blood sugar and bilirubin in the serum all were normal. The concentrations of cholesterol and total lipoids were, respectively, 137 and 415 mg. per 100 cc. of plasma. The bromsulfalein test of hepatic function did not disclose retention of dye. Exton glucose tolerance test revealed that the concentrations of blood sugar were, respectively, 107, 179 and 260 mg. before, one half hour after and one hour after administration of glucose. Sugar did not appear in the urine during the test. The weight was 156 pounds (70.8 kg.) and, all in all, the patient was in relatively satisfactory condition.

*Comment.*—Case 3 illustrates again that chronic relapsing pancreatitis presents the same features both when it is and when it is not associated with disease of the biliary tract. This we shall discuss in detail later. Case 3 also illustrates that the attacks may be of great severity and long duration; that the disease tends to be progressive, as indicated by the increasingly frequent attacks, or even by the appearance of constant pain with daily exacerbations, calcification, diabetes and steatorrhea; that chronic relapsing pancreatitis may produce apparent obstruction of the common bile duct, as indicated by resistance to the passage of probes into the duodenum; that pancreatic enlargement may be sufficient to permit palpation, and that an excessive loss of fat in the stools may occur as it did in this case when constipation is present. The failure of the common bile duct to dilate greatly may be attributed to the thickened walls. It is interesting to note that the attacks were of great severity and duration from the onset of the disease and these characteristics of the attacks were present both before and after cholecystectomy. The pancreatitis gradually subsided after choledochoduodenostomy but recurred from time to time, usually after the patient indulged in the use of alcohol.

#### ANALYSIS OF CASES

##### *Incidence*

Of the 27 patients of this series, 19 were males and 8 were females. The youngest age of onset was 10 years, the oldest 75 years and the average age 41.1 years. In 7 the disease began before the age of 30. A familial incidence was not noted. The average weight of the 19 patients of this group about whom the information on previous weight was available was 13 pounds (5.9 kg.) above the standard weight at the onset of the disease. Five patients averaged 7.8 pounds (3.5 kg.) below, and 14 patients averaged 20.5 pounds (9.3 kg.) above, the standard weight. Chronic relapsing pancreatitis whether with or without associated disease of the biliary tract affects males more frequently than females, begins at any age and does not exhibit a predilection for the markedly obese.<sup>1</sup>

##### *Possible etiologic factors*

*Alcohol.*—In 11, or 50 per cent of the cases in which data were available, alcohol was used. Six of these individuals used it heavily. In 1 case, overindulgence in alcohol incited painful seizures.

*Other factors.*—Nervous tension was stated as an inciting factor in the painful seizures in 1 case, excitement in 1 case, the ingestion of greasy or spicy foods in 5 cases and the ingestion of raw apple in 1 case.

*Early manifestations*

Remarkably few notations were made in the records of the cases of this series about symptoms preceding the first of the recurring painful seizures. In 2 cases it was stated that dyspepsia did not precede the first attack of pain. In 4 cases gaseous distress after eating fats occurred for periods ranging from one week to thirty years prior to the first of the series of painful attacks. Another patient had epigastric pain and heartburn for twenty-five years while still another had nausea and gnawing epigastric distress, which was eased by soda, for two years before the first attack of pain. In the remaining 19 cases pain was the first symptom mentioned. Dyspepsia or low-grade pain may precede the first painful seizure but most frequently an acute and painful seizure heralds the onset of the disease.

*The painful seizure*

The painful seizure is the most typical and, of course, the most violent and arresting manifestation of the disease.

*History.*—The shortest history for painful seizures was three months, the longest thirty-four years and the average 7.5 years. Five patients had seizures for five to ten years and 10, or 37 per cent of all the cases, had seizures over a period of ten or more years.

*Character of pain.*—Pain was variously described as cramping in 6 cases, stabbing in 1, colicky in 5, steady in 3, sharp in 4, dull and aching in 4, knifelike in 1, constant in 1 and excruciating in 2. In 5 cases the character of pain was not described. Unhappily, the character of the pain does not indicate the nature of the underlying disease.

*Mode of onset of pain.*—In 11 of the 27 cases, the onset and development of pain was stated as sudden and severe. In 4 cases it was gradual and in 12 cases information was lacking.

*Frequency.*—The frequency of painful seizures varied considerably not only among patients but also in the individual patient. They occurred as infrequently as once every four years and as often as once daily or weekly. In 14 cases there was a progressive increase in the frequency of attacks. For example, in 1 case the patient had three to four attacks a year in 1926, increasing to an attack once a week in 1933 and finally an attack every four or five days in 1940. This tendency toward more frequent attacks with the lapse of time seems to be a common feature of relapsing pancreatitis.

*Severity.*—In 3 of the 27 cases pain was relatively mild, moderate in 1 case and severe in 23 cases. Pain was relatively mild throughout the disease in 1 case, mild at first but later severe in another case, severe at first and milder

subsequently in 2 cases, progressively more severe in 3 cases and severe throughout the course of the disease in 12 cases. In 6 cases, as in illustrative case 3 there was progression to almost continuous pain. The pain of pancreatitis is not only just as severe as that due to biliary colic, but often lasts much longer and therefore may require repeated hypodermic injections of morphine. In 2 cases pain became so severe and frequent that morphine was required daily. One patient experienced some relief from emesis, another from belching and from ingesting soda and 2 from passing flatus. One patient obtained relief by pressure over the abdomen. In short, the painful seizures usually were severe, occasionally mild or moderate, tended to increase in severity, but sometimes became less severe with the passage of time. Fatty foods, exercise and excitement seemed to aggravate the pain in some individuals.

*Location of pain.*—The primary or initial site of pain was in the epigastrium in 11 cases, right upper quadrant of the abdomen in 9 cases, left upper quadrant in 3 cases, over the entire upper part of the abdomen in 1 case, left lower quadrant in 1 case, across the lower part of the abdomen in 1 case and in the lower thoracic and upper lumbar portions of the back in 1 case. The primary location of the pain is most suggestive of pancreatic involvement when it is in the left upper quadrant.

*Extension of pain.*—Pain extended to the left subcostal region in 6 cases, to the right subcostal region in 3, posteriorly to the back in 17, to the entire abdomen in 3, to the left anterior part of the thorax in 2, to the lower anterior part of the thorax in 5, to the right scapular region in 4 and to the left shoulder in 3. Extension to the symphysis pubis in 1 and to the arms in another case is unusual. When the extension is to the left upper quadrant of the abdomen, to the left anterior part of the chest, to the left shoulder and left side of the back, the possibility of pancreatitis is suggested.

*Duration of pain.*—Painful seizures lasted from one to five hours in 5 cases, from two to six days in 8, from seven to thirteen days in 5, from fourteen to twenty-one days in 1 and in 6 cases the duration was not given. In 1 case the pain lasted "several hours" and in another "several days." Thus, in 15 cases the seizures lasted for a matter of days. Duration of a painful abdominal seizure for days, not hours, is a characteristic that points to something more than uncomplicated biliary colic as a cause. The disease may be pancreatitis. This is similar to the findings in previously reported series of cases of chronic relapsing pancreatitis in which disease of the biliary tract was not present.

#### *Associated symptoms*

The following symptoms were associated with the painful seizures of pancreatitis: nausea in 14 cases, vomiting in 19, constipation in 4, diarrhea in 6, fever in 9, rigors in 10, jaundice in 15, abdominal distention in 7, abdominal

soreness in 3, borborygmi in 2, shock in 1, dysphagia in 1, pruritus in 2, gross hematemesis or melena in 4 and weakness in 5.

Between the acute attacks the following symptoms occurred: intolerance to fatty foods in 8 cases, raw burning epigastric distress in 2, bloating gaseous distress in 6, epigastric pain late after meals in 1, nausea in 3, a constant aching in the epigastrium in 3 and a pressure pain in the left subcostal region in 1. Appetite was poor in 2 cases. Weakness, often quite marked, was a complaint in 7 cases. Constipation was present in 6 cases, being so marked as to overshadow all other symptoms in 1 case. Alternating diarrhea and constipation were present in 1 case. Diarrhea in 3 cases and emesis in 1 case were interval symptoms. Gross gastro-intestinal hemorrhage (either hematemesis or melena or both) was an interval symptom definitely in 4 cases and probably in a fifth. There were no interval symptoms in 2 cases. None of these symptoms are distinctive of the underlying pancreatitis.

#### *Physical findings*

Thirteen patients were examined during or shortly after an acute attack of pain. Body temperature was elevated in 6 cases, with values ranging from 99.4° to 105°F., the average being 100°F. Jaundice was noted in 8 of the 13 cases. Tenderness was noted in the epigastrium in 8 cases, in the right subcostal region in 5, in the left subcostal region in 1 and in the left lower quadrant in 1. Abdominal rigidity was noted in 3 cases. Pancreatic cyst was felt in the left upper quadrant in 1 case. A mass of uncertain origin was felt in the right upper quadrant in 1 case, in the epigastrium in 1, in the epigastrium and left upper quadrant in 1 and in the left upper quadrant in 1. Pallor was observed in 2 cases, cyanosis in 1, emaciation in 1, abdominal distention in 1 and audible peristalsis in 1. The liver was enlarged in 7 cases, being considerably enlarged in 3 cases.

Fourteen patients were examined in the interval between attacks of pain. Jaundice was present in 4 cases. Tenderness in the upper part of the abdomen was observed in 6 cases. A pancreatic cyst was felt in 1 case and an indefinite mass was noted in the upper part of the abdomen in 2 cases. Hepatomegaly was observed in 3 cases, pallor in 1 and pruritic excoriations in 2.

Most of the patients exhibited evidence of weight loss, the average loss being almost one fifth of the original body weight. Thus, in 23 cases in which data were available, there had been an average loss of 28.9 pounds (13.1 kg.) since the onset of the painful seizures. This represents an average loss of 19.7 per cent of the original body weight and is comparable with what occurred in the cases of primary chronic pancreatitis, in which the patients lost 15.7 per cent of their original weight.<sup>1</sup>

### Laboratory data

*Tests of islet function.*—Tests for glycosuria and glucose tolerance and determination of values for fasting blood sugar are of importance in detecting disturbance of the islet cell function in cases of suspected pancreatitis. In only 3 of the 27 cases of this series was glycosuria noted, and in only 3 of the 10 cases in which the fasting concentration of blood sugar was determined was it greater than 120 mg. per 100 cc. In the 3 cases in which both glycosuria and hyperglycemia were present, the disturbance of islet cell function was not transitory but persisted between the acute attacks. Tests of glucose tolerance were done in 4 cases other than the 3 in which there was frank diabetes. In 2 cases the results of the test of glucose tolerance were positive, and in 2 additional cases the results were negative. In 1 case the positive character of the test might well have been due to the inadequate food intake preceding the test, and a diagnosis of diabetes was not substantiated by subsequent observation. In the second case, however, the test repeatedly gave positive results, justifying a diagnosis of mild diabetes.

*Tests of acinar function.*—Determination of values for amylase and lipase in the serum, of the existence of grossly fatty stools, of excess amounts of fat by microscopic examination of the stool and of values for fecal solids, fat and nitrogen by chemical analysis, of the volume, bicarbonate and enzymatic concentration of the duodenal contents after stimulation with secretin are the currently used methods of determining alterations of the internal and external secretion of the acinar cells.

Values for amylase in the serum were found elevated in 3 of the 18 cases. The values were elevated in 3 of 9 cases in which the test was done during the acute phase of the painful seizures and were within the normal range in 9 of 9 cases in which the test was done between painful seizures. Similarly, values for lipase were found elevated in 3 of 7 tests performed during acute seizures and in none of 8 tests performed between seizures. The values for the two enzymes were not always simultaneously elevated, pointing to the value of doing both diagnostic tests. Negative results during acute episodes do not exclude pancreatitis.

The secretory response of the pancreas to stimulation by purified secretin was studied in 5 cases. Values below the lowest range of normal were obtained for one or more of the fractions of the duodenal contents in 4 cases and in the lowest range of normal in 1 case.

The gross appearance of the stools was such that it was assumed that steatorrhea was present in 3 cases. Stools were examined for fat in 8 cases. Of 4 patients examined during an acute seizure, 2 had stools with excessive fat, 1 of these determinations being made by microscopic study and the other by

chemical analysis for percentage of fecal solids that was fat. The stools of 4 patients examined between the acute seizures had excessive fat, the values being determined in 2 instances by microscopic study and in the other 2 by quantitative analysis. An excessive amount of fat was considered to be present if more than 28 per cent of the dried weight of the stools represented fat.

*Tests other than those of pancreatic function.*—Urinalysis occasionally disclosed albuminuria, casts, erythrocytes and, in the presence of jaundice, bile. Serologic tests for syphilis gave positive results in only 1 case but there was no etiologic relationship to the pancreatitis. Anemia was not uncommon but it was mild. The value for hemoglobin was less than 12 gm. and averaged 11.1 gm. in 6 cases; the erythrocyte count usually was less than 4,500,000 and averaged around 4,000,000. Macrocytosis may be present in the case in which jaundice is found. Leukocytosis was rare; it occurred only 4 times among 13 patients examined during acute seizures, the values ranging from 10,000 to 25,000 per cubic millimeter, and it was not present in 14 patients examined between seizures. Morphologic study of the leukocytes occasionally disclosed an infectious toxic picture. The percentage of polymorphonuclear leukocytes may be elevated. The sedimentation rate (Westergren method) often was elevated during an acute seizure (6 of 9 tests) and for some time afterward (2 of 5 tests), the elevated rate ranging from 20 to 84 mm. in one hour. Values for blood urea occasionally were slightly elevated. The concentrations of plasma lipoids usually were normal (6 of 7 cases). In 1 case in which damage to the liver existed, the values for cholesterol and cholesterol esters were, respectively, 130 and 44 mg. per 100 cc. of plasma.

Elevation of the concentration of bilirubin, with direct van den Bergh reactions, occurred in 17 of 23 cases in which tests were made, emphasizing the frequency with which latent or overt jaundice was encountered. Values for prothrombin time were slightly increased in 13 of 15 cases in which this test was made.

#### *Roentgenologic data*

Cholecystography was done in only 3 of the 10 cases in which the gallbladder was present at the time of examination at the clinic, because of the acuteness of the process or because of jaundice. Function of the gallbladder was normal in 1, poor in a second and absent in a third. A roentgenogram of the gallbladder region made in 6 cases showed pancreatic calculi in 1 case. Roentgenograms of the pancreatic region made in 7 cases disclosed pancreatic calcification in 5. In order to exclude a renal origin for the painful seizures, excretory urograms were made and served to disclose pancreatic calcification in 1 case.

Roentgenoscopic examination of the stomach and duodenum, performed in

13 cases, gave negative results in 9, showed the duodenum to be fixed in the gallbladder fossa in 1 and disclosed a duodenal deformity which was interpreted as a duodenal ulcer with crater in 2 other cases. In neither of the last 2 cases was duodenal ulcer found at exploration of the abdomen, the deformity being produced by fixation of the duodenum in the fossa of the gallbladder. In a fourth case, a local constriction of the first and second portions of the duodenum that produced partial obstruction was noted and confirmed surgically. Roentgenograms of the colon were normal in 5 cases in which examinations were made, which served to exclude the colon as a cause of the painful attacks.

#### *Preoperative diagnosis*

A preoperative diagnosis of chronic pancreatitis was made infrequently. Prior to arrival at the clinic, diagnoses of "kinked bowel," intestinal obstruction, appendicitis, appendicitis and cholecystitis, together with incisional hernia and intestinal obstruction, cholecystitis, and duodenal ulcer illustrate the wide range of conditions confused with pancreatitis. It is notable that there were 3 operations in 1 case. The first consisted of cholecystostomy and appendectomy, the second, laparotomy for suspected intestinal obstruction and the third, cholecystectomy with repair of a ventral hernia. In another case there were 4 operations—cholecystostomy, repair of a ventral hernia, cholecystectomy and, finally, laparotomy for suspected intestinal obstruction, all without benefit. Prior to registration at the clinic, a total of 28 surgical explorations had been performed on 20 of the 27 patients. The fact that the correct diagnosis apparently had not been made in most of these cases even after multiple surgical explorations serves to emphasize the difficulty of diagnosis or the reluctance of the surgeon to make a diagnosis of pancreatitis.

At the clinic, in this series of patients seen from 1939 through 1943, the incidence of correct preoperative diagnosis has not been high. The preoperative diagnosis at the clinic was entirely correct in only 28 per cent, partially correct (pancreatitis included among other possibilities) in 16 per cent and entirely incorrect in 56 per cent of the 28 cases in which operations were performed. In short, the diagnosis was correctly made or considered a possibility in 44 per cent of the surgical cases, as compared to a figure of 62.7 per cent for the cases of pancreatitis unassociated with cholelithiasis which already have been reported.<sup>1</sup> Diagnostic accuracy has improved greatly since 1943. Various reports in the literature dealing with acute and chronic pancreatitis indicate that the incidence of correct preoperative diagnosis may vary anywhere from 0 to around 40 per cent.

#### *Surgical procedures and results*

In 26 of the 27 cases one or more surgical procedures were carried out on the biliary tract. The primary surgical procedures carried out elsewhere or at the

*clinic* were as follows: In the 1 case in which cholecystostomy was the sole surgical measure death occurred three weeks postoperatively, a time too short to judge results. Of the 13 cases in which only cholecystectomy was performed, in 9 the painful seizures recurred immediately after operation and in 4 they did not recur until, respectively, seven, five, four and eight years had elapsed. Of the 9 cases in which both cholecystectomy and choledochostomy with T-tube drainage were done, in 5 no relief followed, in 1 relief lasted fifteen months and in 3 there had been complete relief for eleven, sixteen and forty-eight months when the patients were last heard from. In the 3 cases in which, respectively, cholecystectomy and partial pancreatectomy, cholecystectomy and drainage of pancreatic cyst, and cholecystostomy and choledochostomy followed by T-tube drainage were carried out, no relief followed. In short, cholecystectomy or cholecystectomy plus choledochostomy was followed by remission of painful attacks of one to eight years' duration in about one third of the cases (8 of 26) and of four or more years in about one fifth of the cases (5 of 26). It remains to be seen whether the relief is temporary or permanent in the few cases in which the painful seizures have not recurred postoperatively. The relief cannot be associated with the type of cholecystitis or the presence or absence of stones, because both acute and chronic cholecystitis with and without stones were present in patients who were relieved as well as in those who were not relieved.

Secondary operations for relief of the painful seizures were performed at the clinic in 17 of the 26 cases. The results have been only partially satisfactory. In 1 case no information has been obtained about the results of choledochostomy and in another case the patient died too soon after choledochogastrostomy to permit judging results. In the remaining 15 cases, the results can be given. In 8 cases choledochostomy was done and T-tube drainage instituted. In 7 of the 8 cases the T tube is known to have been removed, respectively, two, four and five months, five days, and three and a half, eight and four months postoperatively. In 5 of the 8 cases painful seizures had not recurred twenty-four, thirty-six, twenty-four, five and thirty-six months postoperatively. In 3 of the 8 cases the course of the disease was not altered. Thus, the results of choledochostomy and T-tube drainage, prolonged in most cases, has been good so far in 5 of 8 cases. In the remaining 7 of the 15 cases in which results of the surgical procedure are known, choledochoduodenostomy had been followed by complete and immediate freedom from pain in 6 cases when the patients were last heard from, fifty-five, twenty-four, forty-two, thirty-six, fifty-four and fifty-six months postoperatively, and in 1 case operation had been followed by marked but delayed relief from pain. In short, in two thirds of these cases, remission was prompt and the attacks had not recurred when the patients were last heard from. While these results leave

much to be desired, they encourage the performance of similar procedures in attempts to relieve the painful seizures of chronic relapsing pancreatitis.

The results of surgical procedures carried out at the clinic are of interest. Satisfactory relief followed cholecystectomy or cholecystostomy in 3 of 5 cases, choledochostomy with T-tube drainage (gallbladder removed previously) in 4 of 7 cases in which the results were known, and choledochoduodenostomy in 6 of 7 cases. Surgical attack on the biliary tract promises satisfactory relief from recurring painful seizures in a percentage high enough to justify this approach.

#### SURGICAL PATHOLOGIC FINDINGS

In analyzing the pathologic findings of the surgeon, the data have been divided into two groups. In group 1 have been placed those data from the 10 cases in which the gallbladder was in place at the time of exploration at the clinic and in which the pathologic description of the entire biliary tract and pancreas was available for analysis. In only 1 of these cases was a secondary exploration of the biliary tract carried out at the clinic. In group 2 have been placed those data from cases in which the secondary exploration of the biliary tract was carried out at the clinic. In these cases, the data about the pathologic condition of the biliary tract and pancreas at the time of the primary exploration were obtained from the patient, in which instance the information may be inaccurate, or from the surgeon. One case was not surgical but necropsy findings were available.

##### *Pathologic findings in the cases in which the gallbladder was *in situ* at time of exploration at the clinic*

The pancreas was well described by the surgeon in 9 cases. If the activity of the pancreatitis is judged on the basis of the date of the last painful seizure, tenderness, sedimentation rate and enzymatic activity of the serum, along with the clinical features and the pathologic description, then in 1 case the pancreatitis involved the entire pancreas but was of mild degree and inactive; in another case the pancreatitis was active but localized to the tail of the organ, and in still another case the disease had been active three weeks before exploration but mainly involved the tail (cyst contained  $1\frac{1}{2}$  pints [720 cc.] of fluid), there being only slight induration in the head. Thus, in 3 cases the pancreatitis was generalized, mild and inactive or localized and active or recently active. On the contrary, in 6 cases the pancreatitis was extensive and subacute, and clinical evidence of activity was present or had been present shortly before operation. In an additional case, the surgeon simply noted the presence of pancreatitis, and information upon which to base an opinion regarding activity was not sufficient.

The common bile duct was described in the following ways by the surgeon: In 3 cases it was normal to palpation and was not opened and in 5 cases it varied from 8 mm. to 2 cm. in diameter but obstruction to the passage of a probe through the duct into the duodenum was not encountered. The absence of obstruction was confirmed by choledochogram in 2 cases but the thickness of the walls of the common bile duct was not described. In 1 case the common bile duct was 1.5 cm. in diameter and at exploratory choledochostomy obstruction to passage of a probe from the duct into the duodenum was encountered. A choledochogram was not obtained in this instance. In the remaining case, data about size and obstruction of the duct was not recorded but it was the seat of cholangitis. The gallbladder was distended in 1 case in which resistance to passage of a probe was encountered. Stones were not found in the common bile ducts in the 10 cases. It is of special interest that both the common bile duct and the gallbladder were dilated without demonstrable organic obstruction of the common bile duct.

As one would expect, the changes in the common bile duct appear to bear a relationship to the condition of the pancreas. Thus, in 3 cases in which the common bile duct was normal to palpation the pancreatitis was of a degree, extent and location unlikely to produce secondary obstruction or dilatation of this duct. On the contrary, in those cases in which the common bile duct was dilated with or without obstruction the pancreatitis was extensive, involving the head as well as the remainder of the gland.

A history of jaundice was obtained in 5 cases, jaundice was noted in 4 cases, the concentration of bilirubin was elevated respectively to 1.7, 1.3, 2.7, 4.0, 2.2, 2.5 and 2.8 mg. per 100 cc. in 7 cases and the van den Bergh reaction was direct in those cases in which the common bile duct was dilated. The contrary was true in the cases in which the common bile duct was normal in size. Jaundice occurred in 1 case in which resistance to the passage of the scoop from the common bile duct into the duodenum was demonstrated as well as in 5 cases in which such resistance was not demonstrated. Jaundice apparently may appear as a result of anatomic or physiologic obstruction of the common bile duct.

The condition of the liver was described in 3 cases. In 1 case in which there was jaundice and a history of jaundice and the common bile duct was normal in size, the liver was normal in appearance. In another case, in which a history of jaundice and jaundice were present and the common bile duct was enlarged, the liver was said to be enlarged but its surface was smooth. In still another case, in which a questionable history of jaundice was obtained and in which jaundice was not noted but the concentration of bilirubin was 1.7 mg. per 100 cc., marked hepatitis was present. As might be expected, damage to the liver seems to result from obstruction of the common bile duct.

The pathologic changes in the gallbladder appear to bear a relationship to the pathologic changes in the common bile duct and pancreas. The surgeon stated that the walls of the gallbladder were thicker than normal in 1 case, slightly thickened in 1 case, chronically diseased (stones) in 1 case, and mildly, subacutely diseased (multiple stones) in 1 case. In these 4 cases the pathologist found minimal evidence of chronic cholecystitis; the disease in the pancreas was chronic, diffuse but inactive or localized to the tail and recently active, and the common bile duct was normal in size or only very slightly dilated.

In another 4 cases, the surgeon stated that the gallbladder was thick-walled, edematous and subacutely inflamed in 1 case; that the gallbladder was distended, its walls thickened in 1 case; that it was distended four times normal size, the seat of chronic cholecystitis, grade 2, and filled with foul mucopurulent bile in 1 case, and that its walls were thickened and contained multiple stones in 1 case. In these 4 cases the pathologist found a moderate degree of chronic inflammation of the gallbladder as evidenced by fibroblastic proliferation and a moderate number of lymphocytes. In each of these 4 cases, the pancreatitis was subacute, active or recently active at the time of exploration, as judged by clinical and laboratory data, and in 3 cases the pancreas was subacutely inflamed and the common bile duct was dilated or was the site of cholangitis, as observed at necropsy, but not obstructed. In 2 of these 4 cases there was moderate edema of the wall of the gallbladder, but in no case was there ulceration of the mucosa or actual suppuration. In the other 2 cases the surgeon noted that the gallbladder was distended and subacutely inflamed in 1 case and subacutely inflamed in 1 case. In these 2 cases the pathologic description of the gallbladder was not available but in each case the pancreatitis was recently active and extensive and the common bile duct was enlarged; however, only in the first case did the surgeon encounter resistance to passage of the probe into the duodenum.

The pathologic changes in the gallbladder were relatively minor but appeared to be slightly more marked in those cases in which the pancreatitis was active and extensive and the common bile duct dilated. Dilatation of the gallbladder was accompanied by dilatation of the common bile duct in the 2 cases in which the size of the common bile duct was known, and was noted both with and without obstruction to passage of the probe into the duodenum.

Summarizing, it appears that the pancreatitis may be responsible for dilatation of the common bile duct and dilatation of the gallbladder and that the degree of pathologic change in the gallbladder bears some relationship to the extensiveness and activity of the disease in the pancreas.

Surgical procedures were not carried out in 1 case elsewhere or at the clinic. Because data about the gallbladder, common bile duct and pancreas were obtained at necropsy elsewhere with the gallbladder in situ, these data are

best considered in relation to those of this group. The pancreas was markedly enlarged, indurated and nodular, particularly in the head, measuring 15 by 8 by 5 cm., and contained 2 abscesses and many areas of calcification. The common bile duct was not described. The gallbladder measured 9 by 3.5 cm., was somewhat thickened and contained 1 bean-sized pigment stone.

*Pathologic findings in the cases in which the gallbladder had been removed previously*

The pathologic anatomic descriptions of the gallbladder, common bile duct and pancreas at the time of cholecystectomy performed elsewhere in 16 of the cases are, for the most part, meager. In 3 cases pancreatitis was noted. In 1 case deposits of calcium were present in the pancreas at the time of cholecystectomy. In 4 cases exploratory choledochostomy was performed at the time of cholecystectomy and T-tube drainage was instituted but in only 2 cases was anything known about the pathologic anatomy. In 1 case stones were removed from the common bile duct. In 1 case the common bile duct was normal in size and without obstruction three months after cholecystectomy and eight months before exploration at the clinic at which time the duct was six times normal size. In 5 cases the gallbladder did not contain stones and in 11 cases it contained 1 to 200 stones. Of those 5 cases in which cholelithiasis was not found, it was stated that cholecystitis was present in 3 cases (a strawberry gallbladder with moderately thickened walls was found in 1 of these cases) and a gallbladder with slightly thickened walls was present in 1 case. In addition to stones as evidence of cholezystic disease it was stated that a chronically infected gallbladder with slightly thickened walls was removed in 1 case, that the gallbladder was gangrenous in 1 case and that it ruptured in 1 case. In short, both mildly and extensively diseased gallbladders are known to have been present in these cases.

Data about the pancreas and common bile duct at the time of exploration at the clinic in the 17 cases in which cholecystectomy (16 elsewhere and 1 at the clinic) had been performed previously were quite complete. In 5 cases the pancreatitis appeared to have been limited to the head of the organ; in 1 case the head was "the size of an orange," in 1 case the head contained a "firm mass," in 1 case the head was "firm," in 1 case "the head contained a cyst 10 cm. in diameter" and in 1 case the head was "enlarged and firm." In the remaining 12 cases the entire pancreas was involved. It was small in 1 case, enlarged in 4 cases and indurated or hard in 8 cases; it contained calcium deposits in 4 cases and multiple small cysts in 1 case. The process was more marked in the head in 4 cases. In only 2 of the 17 cases did the condition of the pancreas, the presence of fat necrosis or existence of lymphadenitis indicate a subacute process. In 1 case the pancreas was subacutely inflamed,

exhibiting woody edema and fat necrosis. In 1 case the pancreas was markedly indurated, and fat necrosis and lymphadenitis were noted. In 1 case the calcium deposits were present to indicate the chronic nature of the process. The process in the pancreas for the most part seemed to be chronic.

Pathologic findings indicative of a subacute pancreatitis were absent in 15 of the 17 cases. It is of interest that of these 15 cases, exploration was carried out in 10 cases during or within a few days of a painful seizure, that value for enzymes in the serum were increased in 4 cases and that jaundice was measurable in 9. In other words, in spite of absence of gross lesions of the pancreas at surgical exploration, indicating recent activity, clinical and laboratory evidence of recent activity did exist in 9 of 10 cases. Recent attacks of pain had not occurred in 5 cases. In these cases, clinical and laboratory as well as pathologic evidence of activity all were lacking. Apparently surgical inspection may not reveal evidence of activity in the pancreas which is chronically inflamed.

The common bile duct was described in 16 of the 17 cases. In 2 cases the duct was normal in size and in 2 cases it was only slightly enlarged in spite of previous cholecystectomy. In the remaining cases the common bile duct was enlarged one and a half times to six times normal size and up to 2.5 cm. in diameter. Its walls were thickened in 7 and thin in 2 cases. It was definitely stated that probes were passed from the duct into the duodenum without encountering resistance in 7 cases and with resistance in 2 cases. Also in the remaining cases exploratory choledochostomy was carried out but no specific mention of obstruction or absence thereof was made. Choledochograms were done in 6 cases without demonstrating obstruction. Choledochostomy with T-tube drainage was the operative procedure in most cases; choledochoduodenostomy was done in 5 cases in which the diameters of the ducts were, respectively, twice normal size, two to three times normal size, 2.5 cm., six times normal size and 2.5 cm. In 1 case stones composed of calcium carbonate were removed by way of the common bile duct. The composition of the stones suggested pancreatic rather than cholelithic origin.

Latent or overt jaundice was present in 10 cases. The concentration of bilirubin in the serum in these cases was, respectively, 4.8, 6.6, 1.9, 1.0, 6.7, 2.3, 1.9, 1.4, 3.3 and 2.7 mg. per 100 cc. In each case the van den Bergh reaction was direct. In 2 cases the common bile duct was normal in size or slightly dilated and unobstructed by the pancreas; in 5 cases the duct was moderately or greatly dilated and not obstructed and in 2 cases the common bile duct was enlarged and presumably unobstructed. In 1 case the duct was dilated and obstruction was present. In these cases jaundice apparently was rather infrequently due to mechanical obstruction. In the absence of anatomic obstruction, physiologic obstruction due to involvement of the wall of

the duct, such as is seen in carcinoma of the head of the pancreas, must be postulated to explain the jaundice and, in some cases, the degree of dilatation of the duct.

The appearance of the liver was described in 12 cases. It was normal in 6 cases. It is especially interesting that the appearance of the liver was normal in 3 cases in spite of jaundice and dilatation of bile ducts. The following descriptions were applied to the livers, respectively, in 4 cases: dusky, greenish and rounded, dusky and slightly firmer than normal. That some degree of liver damage was present was not surprising in these cases because of the dilatation of the common bile duct and a history of jaundice (3 cases) or the presence of jaundice. Most interesting were the findings of a "dusky" liver in 1 case and of an "inflamed appearing liver with a pink-brown color" in 1 case, both cases in which dilatation of the common bile duct, jaundice was not noted. The changes cannot be ascribed to obstruction of the common bile duct and back pressure on the liver and they raise the question whether the inflammatory process in the pancreas can spread to the liver as it may spread to the peripancreatic tissues and elsewhere.

In summary of the pathologic changes noted by the surgeon it can be said that the pancreatitis may be localized to the head or to the tail of the organ but usually involves the entire gland. The pancreatitis may be described as chronic or subacute with or without fat necrosis or lymphadenitis. The pancreas usually is enlarged, sometimes greatly so, but it may be small; it also is indurated, sometimes nodular, and may contain abscesses, cysts or deposits of calcium.

The common bile duct may be normal in size, its walls normal in consistency, but more often it is enlarged, its walls thickened. The dilatation of the common bile duct often is more than can be accounted for by compensatory dilatation occurring with nonfunction of the gallbladder or cholecystectomy. Probes and scoops often are passed from the common bile duct into the duodenum without encountering resistance, even when the dilatation is great, but occasionally resistance of a degree to indicate obstruction is encountered. In either event the pancreatitis appears responsible. When obstruction is not present, the dilatation presumably may be due to "physiologic" obstruction arising from involvement of the wall of the common bile duct by the inflammatory process and is similar to that seen in carcinoma of the pancreas that does not produce organic closure of the common bile duct. Presumably, when obstruction is present the inflammation due to pancreatitis not only has invaded the wall but also has caused narrowing of the lumen as a result of pressure. Choledocholithiasis appears to be an infrequent finding.

All grades and types of cholelithic disease are found. The cholecystitis often is minimal and chronic, but may be acute, or subacute. Acute or sub-

acute cholecystitis may accompany subacute or acute pancreatitis. Gangrene and rupture may occur. The gallbladder, in the absence of obstruction of the cystic duct, may be distended, sometimes greatly so. In such cases organic, not physiologic, obstruction of the common bile duct is noted.

Commonly, it is assumed that pancreatitis is secondary to cholezystic disease. We have pointed out previously, in studying the pathologic findings in a series of cases in which we did not believe the degree of cholezystic disease to be great enough to influence the clinical picture, that the pathologic changes noted may well be secondary to the pancreatitis.<sup>1</sup> Thus, we pointed out that the frequently described dilatation of the gallbladder and duct was not primarily a disease of the structures but of increased pressure in the extrahepatic biliary tract, obstruction of the cystic duct excluded. We also pointed out that the degree of cholecystitis present was far too minor to explain the severity of the symptoms, the associated dilatation of the common bile duct and the history of jaundice in one or more attacks of pain. Finally, we pointed to a case in which excellent function of the gallbladder was demonstrated by cholecystogram, in which edema of the gallbladder was found at exploration but in which only very mild disease of the gallbladder was noted at necropsy performed weeks after the last painful seizure; all this was given as evidence that the edema of the gallbladder may be transitory and possibly secondary to the pancreatitis. In short, we presented evidence favoring the view that the changes noted in the biliary tract in these cases may be secondary to the pancreatitis. We also presented cases of chronic pancreatitis without cholezystic disease. In this study we have again noted the marked changes in the biliary tract logically attributable only to the pancreatic disease. A belief that the unquestioned cholezystic disease present in these cases is primarily responsible cannot be complacently accepted as the starting point of the pancreatitis in all cases. The alternate theories that infection or inflammation in the pancreas affects the gallbladder secondarily or that the process appears simultaneously in the two organs should be examined with care.

#### PATHOLOGIC ANATOMY

Observations concerning the gross pathologic appearance of the pancreas at the time of surgical exploration already have been summarized. Tissue for histologic study was made available by biopsy in 6 cases and at necropsy in 1 case. Fibroblastic proliferation and fibrosis were prominent features of all sections of the pancreas examined. Interlobular fibrosis was more pronounced than intralobular or interacinar fibrosis. In 2 cases the biopsy did not reveal a lobular arrangement of pancreatic parenchyma but only masses of fibrous connective tissue. In 2 cases residual regions of necrosis were observed (fig. 1) with early pseudocyst formation.

The acini, when present, were atrophied and disorganized (figs. 2 and 3a). Frequently they appeared as small groups of cells without the normal arrange-



FIG. 1. PANCREAS

a. Residual region of necrosis with organization and early pseudocyst formation (H and E  $\times 110$ ). b (case 24). Early pseudocyst formation (H and E  $\times 170$ ).

ment around a central lumen. The islands of Langerhans were frequently atrophied. Separation of the islets as if by edema, fibrosis and degeneration was observed (fig. 3b). Sometimes the cells are arranged in lobules which were widely separated.

A survey of the histopathologic features of the pancreatic lesions in these cases discloses the fact that they differ in no manner from those previously

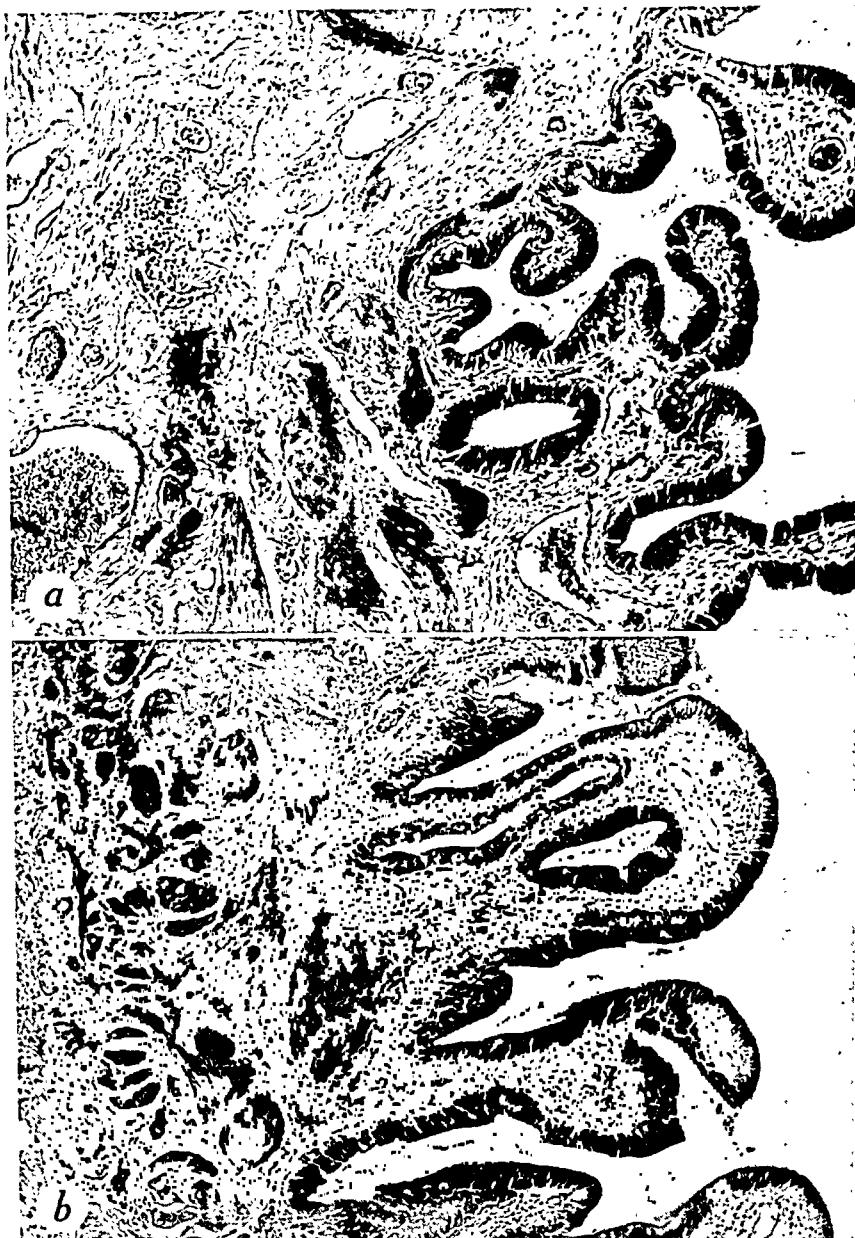


FIG. 4. GALLBLADDER

a. Mild chronic cholecystitis (H and E X75). b. Moderate chronic cholecystitis with edema of the wall (H and E X60).

described in primary chronic relapsing pancreatitis. So far as the histopathologic aspects are concerned, the two groups of cases might be considered as a single entity. This study again suggests that chronic relapsing pancreatitis may represent the summation of repeated attacks of acute interstitial pancreati-

tis, or repeated sublethal attacks of so-called acute hemorrhagic pancreatitis, or perhaps in some cases, a combination of both types of pancreatitis.



FIG. 5. PANCREAS

a. Groups of atrophied acini surrounded by fibrous connective tissue (H and E  $\times 95$ ). b. Fibrosis and perineural collections of lymphocytes (H and E  $\times 115$ ).

If we grant that there are no anatomic or histopathologic differences in the two groups of cases the question may still be asked as to whether or not these cases differ from a pathogenetic standpoint. In other words, was the pancreatic lesion secondary to an inflammatory process in the biliary tract? As

has already been pointed out, the evidence from the observations at the time of operative exploration is not very convincing. The histopathologic evidence also gives very little support for such a concept. In the 2 cases in which the inflammatory processes present in the gallbladder and pancreas could be compared at the same time there was no evidence that the cholelithic disease preceded the pancreatic lesion. On the other hand, the lesion in the pancreas in 1 of these cases appeared older and had been much more destructive than the lesion in the gallbladder. The latter revealed only a few lymphocytes scattered through the wall and a mild cholesterosis. In the other of these 2 cases a moderate degree of cholecystitis was present but again the inflammatory process in the pancreas appeared just as old, or older, and had certainly been more destructive, with considerable loss of parenchyma, fibrosis and abscess formation. It would also seem significant that in one half of the 8 gallbladders examined the inflammatory process was of the mildest degree with only a scattering of lymphocytes to indicate the presence of an inflammatory process.

In summary, therefore, the histopathologic survey gives no support to the thesis that the pancreatic lesions were secondary to cholelithic disease. On the contrary, if any conclusions at all can be drawn from this study they would point to the probability that the inflammatory processes in the pancreas preceded or occurred at the same time as the inflammation of the gallbladder. In other words, instead of the old concept that inflammation of the biliary tract is the precursor of pancreatitis it may well be that the lesions of the biliary tract follow and are the result of a primary inflammation in the pancreas or that the two conditions may occur simultaneously and independently of one another.

#### TERMINAL ASPECTS

To date, 5 patients have died. One died of massive gastro-intestinal hemorrhage five weeks after cholecystostomy and subsequent formation of gastric and fecal fistulas. Another died three weeks postoperatively of pylephlebitis and peritonitis found at operation. A third died of cardiac failure, and a fourth of gross gastro-intestinal hemorrhage when under treatment at a hospital for addiction to narcotics. In a fifth case the cause of death is unknown.

#### COMMENT

Comparison of the clinical, clinicopathologic and pathologic features of chronic relapsing pancreatitis with associated cholelithic disease, as exhibited in the 27 cases of this series, with those of chronic relapsing pancreatitis not associated with disease of the biliary tract, as exhibited in the 29 cases of a series recently analyzed and reported,<sup>1</sup> discloses many similarities and remarkably few dissimilarities. First, the anatomic and histopathologic features of

the disease in the pancreas are essentially the same in the two series of cases. Interstitial fibrosis and residual necrosis are rather constant findings. Cyst and abscess formation and deposition of calcium occur in both. In each series, the pancreatitis most often involves the entire organ, may be largely localized to the head, body or tail, but shows no distinct tendency to involvement of that part of the pancreas in close proximity to disease of the biliary tract, that is, the head, when disease of the biliary tract is present.

Second, chronic relapsing pancreatitis regardless of the presence or absence of disease of the biliary tract involves males more frequently than females and begins at all ages. It is interesting that the average weight of the patients with disease both of the pancreas and of the biliary tract (13 pounds above normal) was only slightly greater than that of those with disease of the pancreas alone (4.7 pounds) and that alcohol becomes an etiologic suspect in both series. The sex and weight incidence is in contradistinction to that observed in cases of cholelithic disease alone.

Third, the clinical features of chronic relapsing pancreatitis are essentially the same in the two series. One might anticipate that dyspepsia of the cholelithic type before the onset of and between painful seizures, and attacks of pain of a few hours' duration localized in the right upper portion of the abdomen and epigastrium would be more frequent when cholelithic disease was present. No such tendency to reflect the presence of cholelithic disease was recorded in the case records. Both in the cases of chronic relapsing pancreatitis with cholelithic disease and in those without it the tendency of the painful seizures to last days, not hours, is that feature of the seizure which arouses suspicion of something more than uncomplicated biliary colic as its cause. Primary localization of the pain in the left upper quadrant of the abdomen and extension to the left upper quadrant, left anterior part of the chest, left side of the back and left shoulder, thus suggesting something more than cholelithic disease, occurred with about the same degree of frequency in the two series; moreover, physical and laboratory findings in the two groups of cases were similar. However, cholecystography performed in a larger series of cases in which the diseased gallbladder had not been removed at the time of examination and in the interval between attacks of pain and jaundice should disclose the cholelithic disease such as was found in the present series.

Fourth, the same sequelae, due to involvement of the pancreas, appear regardless of the presence or absence of cholelithic disease. It is of interest to note, however, that in the series without and with disease of the biliary tract, diabetes appeared, respectively, in 7 and 3 cases, gross steatorrhea in 8 and 3 cases, and calcification in 14 and 6 cases, but larger series must be studied before it can be concluded that in the patients with cholelithic disease these sequelae are less prone to develop.

Fifth, the most frequent sequela due to pressure of the enlarged pancreas on the neighboring structures is dilatation of the common bile duct, both in the series with and in the series without disease of the biliary tract. In many of the patients with disease of the biliary tract the dilatation was minor in degree and possibly due to compensatory dilatation following cholecystectomy. In both types of case, dilatation unaccounted for by this factor occurred. In both series of such cases, obstruction to passage of the stool was noted in some cases and not in others. When obstruction is not noted the dilatation may be physiologic and due to involvement of the wall of the duct by the pancreatitis. Dilatation of the gallbladder without obstruction of the cystic duct appears both in the series without and in the series with disease of the biliary tract.

Sixth, in cases in which painful seizures occur, the diagnosis of both pancreatitis and cholecystitis in the same patient is made difficult by the similarity of the clinical syndromes of each disease. The most frequently made diagnosis will be cholelithiasis, if for no other reason, because cholelithiasis occurs many times more frequently than does pancreatitis. However, it seems clear that pancreatitis, as well as complications of cholelithiasis, should be strongly suspected when the painful seizures last days, not hours, and especially so when the pain starts in the left upper quadrant of the abdomen and when the pain extends to the left upper quadrant, left anterior part of the chest, left side of the back or left shoulder, even if cholecystitis also is present. It also is clear that pancreatitis is definitely present in cases of disease of the biliary tract when disturbance of acinar and islet function accompanies and follows acute seizures and deposition of calcium can be demonstrated. The appearance of a rounded, cystic mass in the pancreatic region during the painful seizure, or soon thereafter, may have the same significance as does diabetes, steatorrhea and calcification. Finally, it may be said that a high index of suspicion of pancreatitis, more careful analysis of the features of painful abdominal seizures, and careful investigation of pancreatic function in every instance of acute abdominal seizures will increase greatly the frequency with which the diagnosis of pancreatitis is made. Once the diagnosis has been made, the clinician should investigate for evidences of past pancreatitis and be on the lookout for recurring attacks and sequelae of pancreatitis because pancreatitis is often a recurring and progressive disease.

The diagnostic problem varies with the acuteness of the process and the presence or absence of the gallbladder. When a patient whose gallbladder has not been removed previously is seen during an acute painful seizure, the diagnosis of pancreatitis will be suspected if duration and location of the seizure is especially suggestive, and made if the values for amylase and lipase in the serum are elevated, or if steatorrhea, diabetes or calcification are present. The diagnosis of cholecystitis with or without stones will await a satisfactory

cholecystogram which often may not be obtainable until subsidence of the acuteness of the attack and disappearance of jaundice.

When the patient whose gallbladder has not been removed is seen in the interval between repeated acute seizures, a poorly functioning or non-functioning gallbladder with or without stones will confirm the presence of disease of the biliary tract but a diagnosis of pancreatitis will be suspected only when the duration and location of the painful attacks have been suggestive of pancreatitis and proved by the demonstration of diabetes (appearing after repeated seizures), steatorrhea and calcification of the pancreas.

When the patient whose diseased gallbladder has been previously removed is seen during one of a series of acute painful abdominal seizures, or between seizures, the diagnosis of pancreatitis can be made by those clinical and laboratory features suggestive or diagnostic of pancreatitis but disease of the biliary tract can be excluded only by exploration of the biliary tract.

Exclusion of disease of the stomach, duodenum, small and large bowel, kidneys and heart and even of retroperitoneal disease may prove a necessary step in the diagnosis of pancreatitis, especially when the patient is seen in the intervals between attacks and in the absence of diabetes, steatorrhea and calcification. Careful notation of clinical features together with appropriate laboratory data will accomplish this.

Seventh, three possible relationships between cholecystitis and chronic pancreatitis have been considered. 1. Chronic pancreatitis is secondary to cholecystitis. It has been assumed that this is true largely because a high percentage of recognized cases of chronic pancreatitis have been found associated with disease of the biliary tract. The assumption is justifiable especially when disease of the gallbladder, and in particular calculous disease of the gallbladder, has been demonstrated by surgical exploration or by roentgenologic examination before the first painful seizures of chronic pancreatitis. However, in such circumstances it is difficult to prove that the cholezystic disease bears an etiologic relationship to the pancreatitis because it is conceivable that pancreatitis may develop independently of a preexisting cholezystic disease, just as pancreatitis may occur in the absence of demonstrable disease of the biliary tract and even in cases in which the gallbladder is congenitally absent. The exact role of cholecystitis in the etiology of pancreatitis invites further study.

2. The cholecystitis may be secondary to the pancreatitis. Certain pathologic findings suggest that this may be so. Thus, in some cases of pancreatitis of a previously reported series, the gallbladder in the absence of obstruction of the cystic duct was found to be unquestionably dilated at surgical exploration.<sup>1</sup> In such cases, the common bile duct may or may not be enlarged. The dilatation of the gallbladder and the common bile duct could be attributed quite reasonably to physiologic or organic obstruction of the common bile duct as a

result of the pancreatitis, with resultant increase in intraductal pressure. Similarly, in other cases of chronic pancreatitis the gallbladder and common bile duct may be dilated but the wall of the gallbladder also may be edematous and thickened. In such cases again it may be assumed that the dilatation might be caused by increased intraductal pressure resulting from obstruction of the common bile duct. The acute cholecystitis may likewise be due to extension of the process in the pancreas to the gallbladder. This is a possibility because in the occasional case the acute edematous cholecystitis found at operation disappears as the acuteness of the process in the pancreas subsides, leaving a functioning gallbladder according to the cholecystogram, and an essentially normal gallbladder at necropsy, in spite of the recurring attacks of pancreatitis in the interval between surgical examination and necropsy. Certain pathologic changes in the biliary tract might well be secondary to the pancreatitis.

Further careful observation will determine whether or not chronic changes and even stone formation will follow repeated attacks of pancreatitis.

3. Cholecystitis and pancreatitis may occur simultaneously and could well be due to the same etiologic agent. Cases such as the first one reported herein may be so interpreted.

Eighth, removal of the diseased gallbladder is clearly indicated. Other surgical procedures have been followed by partial or complete remission of painful seizures, as was the case when significant disease of the biliary tract was not associated with the pancreatitis.<sup>1</sup> The occurrence of remissions of one to eight years following cholecystectomy or cholecystectomy plus choledochostomy in approximately one third of the cases, of one half to five years following secondary choledochostomy and T-tube drainage or choledochoduodenostomy in approximately two thirds of the patients so treated invites trial of these surgical procedures, to stop both the painful attacks and the progress of the disease. Chronic duodenal obstruction requires some type of sidetracking operation, as does obstruction of the common bile duct; pancreatic cyst requires either internal or external drainage, and abscess, external drainage. Pancreatolithotomy may be feasible.

The acute exacerbation should be treated medically. Ephedrine sulfate and papaverine hydrochloride should be used for relief of pain whenever possible. In the event such drugs do not control the distress, the usual opiates must be resorted to. Intravenous administration of fluids to combat dehydration, hypochloremia, alkalosis and acidosis, as the case may be, decompression of the gastro-intestinal tract and accepted measures for combating shock also are used as indicated. During the acute attacks operation to drain an abscess or pseudocyst rarely is advisable. Between the acute seizures, a bland diet is given and alcohol is forbidden. Diabetes is controlled. Insufficiency of external pancreatic secretion with resulting steatorrhea and azotorrhea is treated

by a high caloric, high protein, high carbohydrate, low fat diet, by substitution therapy in the form of enteric-coated pancreatin tablets, or by both measures.

#### CONCLUSIONS

The clinical picture, the pathologic physiology, the course or the pathologic alterations in the pancreas in cases of chronic relapsing pancreatitis are very constant regardless of the presence or absence of disease of the biliary tract.

The problems of diagnosis of chronic relapsing pancreatitis are increased by the presence of associated disease of the biliary tract; awareness of the possibility of pancreatitis, and familiarity with its clinical features. Roentgenologic findings and tests of pancreatic function should lead to a correct diagnosis in a high percentage of cases.

Treatment of chronic relapsing pancreatitis associated or unassociated with disease of the biliary tract is the same, except that there is need for surgical removal of the diseased gallbladder.

Evidence has been cited supporting the thesis that in chronic relapsing pancreatitis, disease of the biliary tract may be secondary to the disease of the pancreas.

#### REFERENCE

<sup>1</sup> COMFORT, M. W., GAMBILL, E. E., AND BAGGENSTOSS, A. H.: *Gastroenterology*, 6: 239 and 376 1946.

# THE TREATMENT OF NON-SPECIFIC ULCERATIVE COLITIS BY AUTOGENOUS VACCINE; CORRELATED BACTERIOLOGICAL AND IMMUNOLOGICAL STUDIES

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## INTRODUCTION

In the course of a comprehensive study of a group of ulcerative colitis patients we have paid special attention to bacteriological, serological and immunological studies. With these studies as a basis we have administered autogenous vaccines to 35 patients and have attempted to evaluate the therapeutic effectiveness of such treatment. In assessing the usefulness of autovaccine therapy it became necessary to analyze the patterns of the natural history of ulcerative colitis and to consider the criteria for evaluating objectively all therapies of this chronic, recurrent disease.

## METHODS

Blood, feces, smears from the rectum or the sigmoid colon, pharyngeal smears, excretions from the ears, the genitals, etc. were examined by the usual bacteriological methods. Stool and rectal smears were inoculated shortly after being taken on blood-agar, Endo and Kaufmann's medium. Throat or other smears were cultured on blood-agar, liver-broth and Clauberg's medium. After 24 hours incubation at 37°C. all organisms were isolated from the solid media in order to obtain pure cultures; then they were restreaked from liquid to the three original media. The diagnosis of pure cultures was established and suspensions of them were made. Living homogeneous suspensions were tested by autoagglutination with the patient's serum using the usual technique of 1:20 to 1:640 dilutions. Another portion of the suspension in 0.5% phenolized saline was heat killed. For intestinal organisms 60°C. for 1 hour was usually sufficient, seldom was a higher temperature necessary; 56°C. for 1 hour was sufficient for throat organisms. The suspensions in plain broth were checked for sterility over a 3-4 day period. In addition agglutinations of the patient's sera with typhoid O and H antigen, with Flexner, Kruse-Sonne and Shiga-Kruse strains of dysentery were performed.

Skin tests were made from the suspensions of all the cultured microorganisms previously killed and tested for sterility. The original suspension was diluted to make the final concentration approximately 1 billion microbes per cc. Of

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this 1 drop was added to 3 cc. of phenolized saline the final concentration then being 5-10 million organisms per cc. Whenever staphylococci were isolated the patient was skin tested with staphylococcic anatoxin in 1:100 dilution. Plain phenolized saline was used as a control. Testing was performed by subcutaneous injection of 0.1 cc. of suspension on the volar surface of the forearm. Reactions after  $\frac{1}{2}$  hour and 24 hours as well as systemic and focal reactions were noted.

### RESULTS

The survey and summary of the results is presented in Table 1.

*Bacteriological findings.*—In our material it has never been possible to grow any of the obligatory pathogens. Potentially pathogenic intestinal saprophytes present in varied amounts and associations were: *E. coli*, *Paracoli*, *Aerobacter aerogenes*, *Pseudomonas*, *Alcaligenes faecalis*, *Proteus* and alpha and gamma streptococcus. *E. coli* occurred most frequently (73% of the feces, 80% of the rectal smears); *Paracoli* was less frequent (33% and 28% respectively) and so was alpha and gamma streptococcus (16% and 33% respectively). The others appeared more rarely. There was no essential difference between the results of the tests of the stools and the rectal smears, except in the case of the streptococci which were more numerous in the rectal smears. Some of the streptococci belonged to the enterococcus group, the remainder were not classified according to Sherman's scheme. Repeated attempts to grow *B. necrophorum* in Fortner's oven failed. The remaining material showed no surprising results. The throat smears showed a normal flora, consisting mainly of cocci.

*Agglutination.*—In view of the fact that ulcerative colitis has often been considered to be of dysenteric origin, it was necessary to pay special attention to the dysentery agglutination tests. The result was positive 13 times out of 37 agglutinations in 27 patients. With one single strain it was positive 7 times, with several strains 6 times. On repeating the tests it was found that the reactions changed so that a positive result became negative and vice versa. Equally frequent and variable was the agglutination with *Eberthella typhi* and paratyphoid B, although there was no reason to suppose that the patients had suffered from the disease.

A relatively frequent agglutination with the dysentery bacilli is not proof of dysenteric etiology. We think it most probable that the titers recorded were not specific because in most cases there was a simultaneous agglutination with antigen of several different strains. Also the results from one and the same patient varied and reactions with the varied *Salmonellae* were equally frequent. Bacteriology and serology alone cannot solve the problem of the relation of ulcerative colitis to dysentery.

TABLE I

*Results of bacteriological, serological and immunological examinations on 31 cases of ulcerative colitis.*  
Fractions represent the results of skin tests, the numerator being the reaction after 30 min., the denominator the reaction after 24 hours. The results of autoagglutination, if performed, are shown below the skin tests symbols.

No.	DATE	AGGLUTINATION REACTIONS	RECTAL SMEARS			SYSTEMIC OR FOCAL REACTION TO SKIN TESTS		
			STAPH. ANA- TOXIN 1:100	MISCELLANEOUS SOURCES				
1	12-29-44	Typhoid O 160+ Typhoid H 20+	-/-	-/-	-/-	-/-	-/+	-/+
2	6-24-43	Not performed	-/-	-/-	-/-	-/-	-/+	-/+
2	11-10-43	Fleiner 160+ Kruse-Sonne 80+	-/-	-/-	-/-	-/-	-/+	-/+
2	4-3-45	Not performed	-/-	-/-	-/-	-/-	-/+	-/+
3	12-1-44	Typhoid O 160+ Typhoid H 80+ Para B 40+	-/-	-/-	-/-	-/-	-/+	-/+
4	2-27-42	Fleiner 20+	160+	+/- neg.	+/- neg.	+/- neg.	+/- neg.	+/- neg.
5	2-6-42	Negative		+/- neg.	+/- neg.	+/- neg.	+/- neg.	+/- neg.
6	11-3-41	Negative	7++ 20+	-/-	-/+ 20+	-/+ neg.	-/+ neg.	-/+ neg.
6	9-8-43	Not performed						-/+
7	12-18-44	Not performed						-/+



TABLE 1—Continued

NO.	DATE	AGGLUTINATION REACTIONS	PHARYNX		FECES		RECTAL SWABS		SYSTEMIC OR FOCAL REACTION TO SKIN TESTS	
			Beta strep.	Alpha strep.	Pneumococcus	Corynebact. Psednudopht.	Neisseria	Staph. aureus	E. coli	
15	4-2-43	Negative								
16	5-30-44	Negative	-/-	-/-	-/-	-/-	-/-	-/-	-/-	++/+
16	9-27-44	Flexner 320+ Kruse-Sonne 320+ Shiga 160+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	++/+
17	1-25-45	Not performed	-/-	-/-	-/-	-/-	-/-	-/-	-/-	+/-
17	11-1-45	Flexner 80+ Kruse-Sonne 40+	-/-	-/-	+/-	-/-	-/-	-/-	-/-	+/-
18	10-10-44	Negative	-/-	-/-	-/-	-/-	-/-	-/-	-/-	+/-
19	4-21-42	Typhoid O 80+ Flexner 640+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	+/-
19	2-1-43	Negative								systemic
19	10-5-43	Not performed								systemic and focal
20	1-27-44	Not performed								
21	12-8-44	Negative	-/-	-/-	-/-	-/-	-/-	-/-	-/-	++/++

21	5-30-42	Not performed	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	+++/++	
22	12-19-42	Flemer 80+	-/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	+/-	
23	4-14-43	Typhoid O 40+	-/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
24	9-30-41	Typhoid H 80+	-/-	-/-	+/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
24	9-30-41	Negative	-/-	-/-	+/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
24	10-14-42	Negative	-/-	-/-	+/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
25	1-22-45	Not performed	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
26	10- 4-44	Negative	-/-	-/-	+/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
27	6-22-43	Negative	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
28	5-28-42	Not performed	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
28	11-10-43	Typhoid H 320+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
29	3- 1-43	Typh H 610+ Flecr 80+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
29	11-10-44	Not performed	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
30	11-10-43	Negative	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
30	9-15-44	Flemer 160+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
		Shiga 80+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	

TABLE 1—Concluded

No.	Date	AGGREGATION REACTIONS	RECTAL SMEARS												STAPH. ANA- TOXIN 1:100	SYSTEMIC OR FOCAL REACTION TO SKIN TESTS	
			FECES						MISCELLANEOUS SOURCES								
31	3- 1-43	Not performed															
31	5-30-44	Negative	-/-														
Total of positive cultures in 52 examinations...			12	30	22	9	23	16	5	8	38	17	4	8	1	17	43
Skin tests																	
Strongly positive.....			0	0	0	0	1	0	1	2	16	9	2	0	0	16	7
Weakly positive.....			3	3	2	3	10	5	2	2	22	8	1	2	0	1	4
Negative.....			9	27	20	6	12	11	2	4	0	0	1	2	1	0	0
Total.....			12	30	22	9	23	16	5	8	38	17	4	8	1	1	25
Autoagglutination																	
Strongly positive.....			0	1	0	0	1	0	0	2	3	0	1	0	0	5	1
Weakly positive.....			0	3	0	1	1	1	1	5	10	5	1	3	1	2	5
Negative.....			0	3	3	1	1	1	2	0	1	8	5	1	0	2	3
Total.....			0	7	3	2	2	4	1	6	20	13	2	5	1	4	27
																	9
																	3
																	6
																	9

Those who maintain the dysenteric origin of ulcerative colitis point out that the dysentery bacilli can be destroyed in the feces by a specific bacteriophage and that the origin of the disease can be determined by the occurrence of this bacteriophage. The bacteriophage for the Flexner type was only found in one case out of 4; in the remaining cases only the bacteriophages for the *E. coli* proper was found. No conclusions can be drawn from this single result because the bacteriophages are ubiquitous and their diagnostic significance is not yet clear.

*Autoagglutination.*—Antibodies which agglutinate strains of cultured bacteria were often encountered in the patients' sera. Approximately 60% of *E. coli* from the feces and 67% from rectal smears stimulated antigen formation. The results from other organisms can hardly be evaluated because only a small number of tests were performed but they are likely to be similar.

*Allergy tests.*—Judging by the results of skin tests there appears to be only little allergy to the throat bacteria. Occasional positive results are no doubt due to the usual catarrhs of the respiratory tract. This correlates with the findings in healthy persons. A reaction to the staphylococcus antitoxin was found more often. This is not surprising since these organisms are so ubiquitous.

On the other hand, skin tests with intestinal organisms are remarkably positive. They almost always reach 100%. Strongly positive tests are found in about 40% of the cases. Only in the case of the streptococci the skin tests were less frequently positive (about 50%).

Systemic reactions after skin testing are characterized by fever, chills or malaise. In focal reactions there is either amelioration (relief) or increase in severity of symptoms. Such reactions were noted in 14 patients. Eleven patients showed a systemic reaction, three a focal reaction and one showed both simultaneously (see Table 1).

*The relationship of allergy to immunity.*—Our results show that allergy and immunity are not interdependent in ulcerative colitis. They often appear together but not always. The preponderance of positive skin tests over the serological reactions in our cases suggests that intestinal commensals elicit allergy more often than immunity.

#### COMMENT

What deductions can be made from these results for the etiology and pathogenesis of the disease?

1. *Relation to dysentery.*—None of the microorganisms which are obligatory pathogens were the primary causative factors in our cases of ulcerative colitis. In this respect all the bacteriological findings were completely negative, whereas the positive serological results were in all probability nonspecific.

2. *The etiological importance of the intestinal commensals.*—There was no single organism which was grown in every case, nor in circumstances where it could be considered the etiological agent. Since the individual microorganisms appear irregularly and on the other hand elicit allergic and immunological reactions, it is concluded that they cause a secondary infection which involves the mucosa after this has been damaged by some other primary cause.

3. *The importance of the focal infection.*—In considering the focal infection our study has been limited to the streptococci since these are practically the only organisms found simultaneously in the throat and in the intestine. These organisms were grown 14 times simultaneously from the pharynx and from the rectum (or feces), the skin tests from both agreeing in 9 cases, (7 times negative, twice slightly positive). In five cases the skin tests did not agree. If any conclusions may be drawn from these results, it can be said that the throat microorganisms do not take part to any considerable extent in pathogenesis. If they played any role the incidence of positive and agreeing reactions would be more frequent in the case of oral and intestinal streptococci. The mere agreement in morphology and growth is not sufficient.

4. *The importance of allergy and immunity.*—In a great majority of micro-organisms grown from the feces and rectal smears it was possible to get positive skin tests and often autoagglutination. The results of the skin tests agree with the findings in other intestinal diseases e.g. "irritable colon"<sup>10</sup>. In contrast to this, positive skin tests are appreciably less frequent in healthy persons<sup>23, 27</sup>; Dorst and Morris<sup>10</sup> state that they occur only in those individuals giving a history of previous gastro-intestinal disturbances. The autoagglutination with the intestinal commensals (*E. coli*) is usually negative, rarely weakly positive, in normal persons.<sup>34</sup>

Since the positive skin tests in our cases were produced by only minute doses, 0.1 cc., and since they caused systemic and focal reactions in some instances, they may be considered to be a proof of allergy. These results, however, are not sufficient to permit the conclusion that this allergy is the etiological factor proper of ulcerative colitis.

Inasmuch as an allergic factor occurs to a similar extent in other intestinal disorders it is likely to be the result of a secondary sensitisation which develops gradually after a close contact of the microorganism with the raw surface of the damaged mucosa. However it may in the course of a gradual development attain a considerable pathogenic importance and play a large part in the clinical symptomatology. This is supported by the clinical picture of the disease which in the beginning, does not show any of the typical signs of general allergy.

*Treatment of ulcerative colitis by autovaccines.*—The presence of a marked allergy to the intestinal organisms in ulcerative colitis patients suggested the therapeutic use of autogenous vaccine. Vaccines and autovaccines have been

used rather frequently in the treatment of colitis and successes as well as failures have been reported equally often. The mechanism of action has been explained in different ways. Those who believe in the infectious origin of this disease use the autovaccine as a specifically immunizing procedure: some use mixed autovaccines composed of many microbes cultivated from the bowels. The mode of administration is either parenteral<sup>9, 16, 21, 31, 35, 37, 38, 40, 42</sup> or local<sup>1, 4, 5, 9, 22</sup>. Others on the other hand, use a monovalent vaccination. The best known is Bargen's antidiplostreptococcic vaccine. Experience with it has been both favorable<sup>2, 7, 12, 18, 20</sup> and unfavorable<sup>30, 35, 40</sup>.

A second group of authors, believing that the nature of ulcerative colitis is allergic rather than infectious, attempts to explain the autovaccination as either specific or non-specific desensitization<sup>3, 13</sup>. Other authors do not ascribe noticeable effect to this kind of treatment<sup>8, 29, 33, 39</sup>.

*Technic of autovaccine.*—The material from all sources was examined bacteriologically as mentioned previously. The pathogenic nature of the cultured microorganisms was examined serologically by autoagglutination and immunologically by skin tests. The autovaccine was prepared by a similar method as used in the preparation of material for skin tests. Only those strains have been used which showed a positive serological and/or skin reaction. The vaccine usually contained one or two strains of *E. coli* and alpha or gamma streptococci; occasionally Paracoli or other common intestinal and throat organisms were included. Staphylococcic anatoxin in 1:100 dilution was added in most instances (Table 1). The first dose depended on the strength of skin reactions, it usually ranged from 50,000 to 2,000,000 microbes per 1 cc. In the first part of the course of vaccine therapy (8-10 ampoules) the dose went up geometrically, in the following ampoules the increase was slower, roughly so that every further dose was 50% stronger than the preceding one. In case of systemic, focal or local reaction a diluted series was interpolated. On the whole 14-28 ampoules were prepared. Injections were given every 3 to 5 days in such a way that 0.1 cc. was injected intracutaneously and the rest subcutaneously. The dosage was determined and the injections spaced so as to avoid systemic focal and local reactions.

*The evaluation of results.*—The complexity of agents which determine the evolution of ulcerative colitis causes great difficulty in the appreciation of the therapeutic results. It is essential first to establish the spontaneous course of the disease.

*The clinical course.*—The course of ulcerative colitis is one of its most typical characteristics. It is particularly clear if the graphical method is used<sup>2, 25</sup>.

The typical course of ulcerative colitis is one of relapses. The disease proceeds in attacks lasting on the average several weeks or months and separated from each other by intervals. During the intervals the disease is more or less

latent, the remission being either asymptomatic or symptomatic. According to the frequency of the attacks we distinguish: a) the *remittent type* in which the attacks come irregularly more often than once a year (34.2% of our patients); b) the *intermittent type* with less frequent attacks (26.4% of the patients); c) the *mixed type* (5.2%).

In contrast to these types of irregular course, we distinguish the following types of regularly relapsing or "*cyclic type*" (26.3% of our patients) in which the attacks appear regularly either once a year: the "*annual type*", twice a year: the "*semianual type*", or every other year: the "*biannual type*".

A *chronic continuous course* is rather rare, being usually only apparent, caused by complicating factors which obscure the spontaneous periodicity. It may be a secondary infection which persists after the actual attack has ended, the irreparable sequelae of a severe condition causing dysfunction of the colon or association with another severe disease (7.9% of the patients on the whole).

In order to evaluate the effect of any treatment it is necessary a) to know the previous history of the disease for enough time to be able to establish the type of the course, i.e. at least two years; b) to make a diagram showing graphically this course (3); c) to judge whether there is a remarkable change after the treatment. This will be possible only in cases of the regularly relapsing and remittent types. The appreciation of other types, especially of the intermittent type, is very delicate because it is never possible to predict the spontaneous evolution. If these conditions are not respected a spontaneous remission may be mistaken for a therapeutic success.

In our case, the evaluation of autovaccine therapy is still more difficult because a certain degree of polypragmasia could not be avoided. In fact the hospitalization, horizontal position, physical and psychological quiet and appropriate diet are themselves important therapeutic measures. The majority of patients could not be deprived of blood transfusions and vitamins. Therefore the evaluation is very difficult. We attempted to decrease this defect by comparing the development of individual attacks with and without vaccine in the same patient.

For these reasons it seems impossible to put down the results in definite tabular form. It seems more exact to describe the results separately following individual types of clinical course. The following types of effect have to be distinguished: a) the effect upon the character of symptoms during the attack b) the effect upon the interval between individual attacks c) the effect on the periodicity of attacks d) the effect on the character of the next attack.

1. *Regularly relapsing course.* Four cases showing regular annual attacks have been observed. All were of severe forms with three showing remarkable cachexia. On rectoscopy rough ulcerations were found. In two patients,

the intervals prior to our treatment were quiet, the other two had lasting mild colitic disorders, but their general state between the attacks was good.

a. *Effect on the attack.* The autovaccine was started in full attack only in one case; the condition improved rather quickly and cleared up before the end of autovaccination.

b. *Effect on the interval.* Of two patients previously having had permanent difficulties, in one the interval following the treatment by autovaccine was entirely quiet with complete healing of the lesions observed proctoscopically. The other showed only partial improvement.

c. *Effect on the periodicity of recurrences.* Two patients in whom the condition was of lasting duration showed no change in the regularly relapsing course. In 2 others, who before the beginning of the treatment suffered only two attacks, the expected third attack did not occur. Since two recurrences, however, do not allow much certainty as to the type of the course, this "success" should be considered with reserve.

d. *Effect on further attacks.* Three patients suffered new attacks; two being considerably milder and of shorter duration than prior to the treatment; in the third no change was observed. The fourth patient to date shows no recurrence. (5 years).

2. *The remittent type.* Twelve cases of this type have been observed with irregularly occurring shorter or longer attacks. The intervals lasted usually only a few weeks, more rarely a few months, but always less than one year. The form of the disease was usually mild. In six, however, a single severe attack occurred between the milder ones.

a. *Effect on the attack.* The autovaccination was started seven times during the full attack. As far as it is possible to make an evaluation in the type of irregular course our impression for at least five times was that the condition was favorably influenced inasmuch as clinical, and usually proctoscopic recovery occurred.

b. *Effect on the interval.* In 6 treated cases residual symptoms either disappeared or improved during the intervals. This was particularly marked in cases which previously had shown continuous mild difficulties.

c. *Effect on the periodicity.* This can be evaluated in 10 cases. In 8 cases the frequency of attacks decreased more or less markedly; in 2, it did not change.

d. *Effect on further attacks.* In 5 cases, following attacks were somewhat milder and shorter than before treatment. In one case there was no change. In 2 other cases too strong doses of vaccine provoked a severe attack.

3. *The intermittent type.* Eight patients of this type were observed. The usual clinical picture was that of a rectal syndrome without systemic reaction.

Previous attacks lasted from 1 to 6 months with the intervals always longer than 1 year, usually 3 or more, with both subjective and objective recovery.

a. *Effect on the attack.* The autovaccination had been started five times during the attack. In 2 of these patients the attack ended shortly afterwards. It was not, however, possible to establish whether it was the result of the auto-vaccine. No noticeable effect was found in the other 2 cases. One patient died.

b. *Effect on the interval.* Only one patient had symptoms during the intervals. Following treatment with autovaccine they disappeared completely.

c. *Effect on the periodicity and on the future attacks.* It is not possible to evaluate them in this type of course.

4. *The chronic type.* In this group 5 patients with a history of disease over one year's duration were observed. Four patients revealing friable mucosae on proctoscopy had no generalized systemic reactions. The fifth patient suffered a prolonged attack of diffuse colitis with advanced cachexia.

a. *Effect on the attack.* In 2 cases, the state following the onset of autovaccine began definitely to improve and cleared up completely both clinically and anatomically. In the third patient the improvement was only subjective; in the fourth, a favorable change became apparent before starting the auto-vaccine, so that its influence cannot be estimated. In the fifth patient who was in an extremely severe condition, improvement developed very slowly and a complete recovery occurred only 6 months later following 2 series of auto-vaccine.

b. *Effect on further attacks.* Later, 4 patients suffered new attacks. In 2 cases these were milder and shorter, once unchanged. The fourth patient had a very severe attack which very likely was due to injecting too strong doses of autovaccines.

5. The autovaccine was used in 6 additional cases of ulcerative colitis. In these cases, however, either the course of the disease or the lapse of time between treatment was too short to permit evaluation of the efficacy.

*Comment.*—On the whole our experience can be summarized as follows: The autovaccination has been found successful in influencing some stages of ulcerative colitis. Its purpose is twofold: curative and preventive. Suitable cases for this kind of treatment are mild and moderately severe cases in the stage of subchronic suppuration and persisting ulcers, where the general evolution is stationary or regressive. However, this treatment must not be started either during a violent attack or when the general condition is poor. The preventive action against the secondary infection is useful in mild cases, in the stage of friability. In suitable cases autovaccine contributes to shortening of attacks and exerts an especially favorable influence upon the character of the interval between them. It frequently helps to remove manifestations of per-

sisting infection and thus changes the type of course from the chronic to the periodic. This can give the semblance of a clinical "cure".

It should be noted that autovaccination has a different indication than treatment with vitamin P-like substances which have proved effective only in the earliest stages of ulcerative colitis<sup>26</sup>.

Autovaccination is a delicate procedure. Rapid results cannot be expected. Much depends upon the choice of patients, upon the preparation of the vaccine and upon the proper interval between injections. Success does not depend upon the number of types of microorganisms, but rather upon the correct choice in a given case. This can be facilitated by autoagglutinations and skin tests.

We did not find the effectiveness of the autovaccine to depend on the age or sex of the patient nor on the duration of the disease.

As far as the mechanism is concerned, we cannot agree that it is only a non-specific shock-effect; reactions in the patient should be avoided. Autovaccination probably specifically combats or prevents secondary infection and sensitization. To what extent autovaccine might influence the basic disturbance is a problem which remains to be solved.

### *Summary*

(1) Thirty one cases of idiopathic ulcerative colitis were submitted to a bacteriological, serological and immunological investigation with the following findings:

(a) None of the well known pathogens were ever found.

(b) The bacteriological examinations revealed various potentially pathogenic microorganisms generally known as intestinal commensals.

(c) The majority of these organisms elicited a definite allergic and immunological reaction.

(2) On the basis of these bacteriological and immunological findings the following conclusions are suggested:

(a) The intestinal commensals as well as other common microbes are not the primary cause of ulcerative colitis but are involved in secondary infection.

(b) The focal-infectious origin seems improbable, at least regarding streptococci.

(c) The allergy established by skin tests is likely to be a secondary sensitization which develops as a sequel to close contact of microorganisms with damaged mucosa.

(d) This allergy, however, may play a significant role in the clinical picture as implied by the focal reactions.

(3) These results support the concept that ulcerative colitis originates as a result of two pathogenic mechanisms.

- (a) A primary lesion of unknown origin.
- (b) A secondary infection and sensitization.

(4) The evaluation of the therapeutic results is very difficult in this disease; this is due to its spontaneously relapsing course. Five types of this course are pointed out in order to make this evaluation easier.

(5) Treatment with autovaccine was used in 35 cases of ulcerative colitis. In our experience the following principles are of the greatest importance: (a) Careful removal of the material from all the infectious foci and also directly from the lesion; (b) serological and immunological examination of the pathogenic nature of the cultured microorganisms (by autoagglutination and by skin tests); (c) Preparation of the vaccine according to these findings; (d) Intra- and subcutaneous administration; (e) Determination of the degree of dilution and spacing of injections as to avoid systemic as well as focal and local reactions.

(6) Autogenous vaccine has been found to be a valuable supportive measure in mild and moderately severe cases of ulcerative colitis. It may also be capable of preventing the transition of the disease process from a mild to a severe form.

(7) The autovaccine is presumed to act upon the secondary infection and sensitization.

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## HYPOPROTEINEMIA AND EDEMA IN THE COURSE OF TROPICAL SPRUE

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### INTRODUCTION

In the period 1942-1945 the writer had the opportunity of studying 1069 patients of tropical sprue in different stages of evolution of the disease among 12,500 Italian prisoners of war stationed in the Camp of Yol, Kangra Valley, India. The clinical and laboratory features and considerations on the etiology, pathogenesis and diagnosis of the condition in this series of cases have been already reported in previous publications<sup>10, 11, 12, 13</sup> to which reference is made. This paper will briefly present some observations on the occurrence and behavior of edema during the course of the illness and especially in its stage of recovery, as they appear interesting enough to warrant a separate presentation.

### CLINICAL FEATURES, LABORATORY FINDINGS AND RESPONSE TO TREATMENT OF THE EDEMA OF THE STAGE OF RECOVERY FROM TROPICAL SPRUE

Of the 1069 patients followed, 153 (14.4%) presented the clinical picture considered to be typical of tropical sprue: pale diarrhea with steatorrhea, secondary deficiency symptoms (glossitis, stomatitis, dermatitis etc.), hyperchromic anemia with megaloblastic arrest of the bone marrow indistinguishable from that usually observed in pernicious anemia; high split/unsplit-fecal-fat and soaps/split-fecal-fat ratios, flat oral glucose tolerance curve, hypocalcemia. The rest of the patients, all considered cases of tropical sprue in mild form or early stages for reasons which have been previously presented<sup>13</sup>, were diagnosed and treated in early stages of the disease before they developed macrocytic anemia.

Among the 153 anemic patients, 129 presented edema, usually of fluctuating type, limited to the ankles, feet and hands with evident postural modifications. Most of the patients complained also of puffiness of the face, especially in the morning. None of them presented important changes in diuresis, albuminuria, enlargement of the heart or hypertension (in fact, a moderate hypotension was found in most of the cases). Occurrence and severity of the edema appeared more related to the degree of anemia (as cases with lower red cells count and higher color index were usually those presenting more extended edema) than

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to the total serum protein level. Determined with a modification of the method of Bierry and Vivario (Guillamin et al.<sup>5</sup>) this was found to be within normal limits in almost all anemic cases irrespective of the presence or not of edema. No facilities were available for the reliable determination of the A/G ratio.

Interesting was the behavior of the edema under treatment. All patients were uniformly kept at absolute rest in bed, put on a low fat, low carbohydrate, high protein diet and treated liberally with yeast ("Marmite" or "Vegemite", 50 Gm. a day) and optimal parenteral doses of liver extract\*. The response to therapy was various. Nine cases did not respond at all to continuous treatment and 4 of them evolved into the chronic stage of the disease while 5 passed into a fatal condition of aplastic anemia. Eight cases, among the most serious ones, required blood transfusions before any improvement could be obtained. Five received an average of 5 ml. of whole blood *per* kilo body weight intravenously by the drip method (40-50 drops per minute) 2 or 3 times at weekly intervals. In three others, because of the difficulty experienced in obtaining donors, only small amounts of blood intramuscularly (20 ml. daily for 20-30 days) were given, surprisingly with the same good influence on the recovery of the patients. The remaining 136 cases responded promptly to the therapy. Four to six days after the starting of treatment a marked reticulocyte crisis was observed (maximum figures from 7 to 48% after 7 to 10 days). In the same period of time the red blood cell count and hemoglobin level (after an initial drop in most of the cases) began to increase, reaching finally normal values about four weeks later. Examination of the bone marrow showed a considerable increase of the percentage of normoblasts mainly at the expense of megaloblasts and erythroblasts at the end of the first week and a normal picture at the end of the second.

More variability was observed in the response of the edema to treatment. In the nine resistant patients, the edema was not modified by liver and yeast therapy (but responded favourably if only temporarily to plasma transfusions). In 69 other cases it improved rapidly disappearing in 7 to 10 days with a corresponding marked and transitory increase of the diuresis. In the remaining 51, the reticulocyte crisis and the improvement of the hematological conditions were accompanied by rapid extension of the edema (some patients gaining as much as 14 to 16 lbs. of weight in the space of 3 to 4 days) usually 5 to 7 days

\* Two different brands of liver extract were used. One, "Lilly's extract", at the dose of 20 U.S.P. units a day for the first week; every third day in the following two weeks and every week thence as a maintenance dose. The other, "T.C.F. Liver Extract", a sheep liver extract prepared by the Teddington Chemical Factory in Bombay and described as containing "most of the B-complex substances present in the original liver" required a double volume to produce the same reticulocyte response and improvement of the hematological values.

after the beginning of treatment with a marked contemporary drop in total serum protein level. Figure 1 presents average values relative to the extension of the edema (judged by the curve of body weight), hematological conditions

TABLE 1

*Relationship of edema to diuresis, reticulocytic crisis, hematological conditions and serum protein level in a case of tropical sprue in the stage of recovery\**

DAYS OF TREATMENT	WEIGHT kmg.	URINARY OUTPUT ml./24 hr.	RED BLOOD CELLS millions per cmm.	Hb	RETICULOCYTES %	SERUM PROTEINS gms. %
1	41.7	870	2.73	62	1.5	6.52
2	42.1	1,010				
3	44.7	800	2.94	57	4.6	
4	47.0	750				6.02
5	49.8	700				
6	51.2	890	3.10	64	19.2	
7	54.8	655				5.31
8	53.2	675				
9	53.8	910				
10	52.1	1,000				
11	52.4	1,055	3.75	72	6.4	
12	50.8	1,075				6.10
13	50.4	1,250				
14	48.9	1,300				
15	59.1	1,350				
16	48.0	1,400				
17	47.3	1,310	3.92	78	2.5	
18	47.5	1,350				
19	46.4	1,500				7.03
20	47.1	1,540				
21	45.3	1,600				
22	42.4	1,750	4.34	84	1.2	
23	41.8	1,350				7.15
24	42.4	1,300				
25	42.8	1,450				
26	44.0	1,350				
27	43.8	1,200				7.04
28	44.1	1,240	4.75	89	1.0	

\* The body weight was considered an indication of the extension of the edema. The intake of fluids was kept constant at an approximate daily level of 56 ozs., throughout the entire period of observation.

and serum protein level, and Table 1 records analytical data obtained in a single average case. The values shown in Figure 1 are given separately for the patients whose edema improved immediately after starting treatment (10 cases) and those in which it showed a temporary extension (also 10 cases). It is evi-

dent that, while reticulocyte crisis and improvement of the red blood cells count were similar in the two groups, in the group characterized by the extension of the edema an almost contemporary drop in total serum protein level occurred. The edema then regressed, slowly at first and then markedly, 20 to

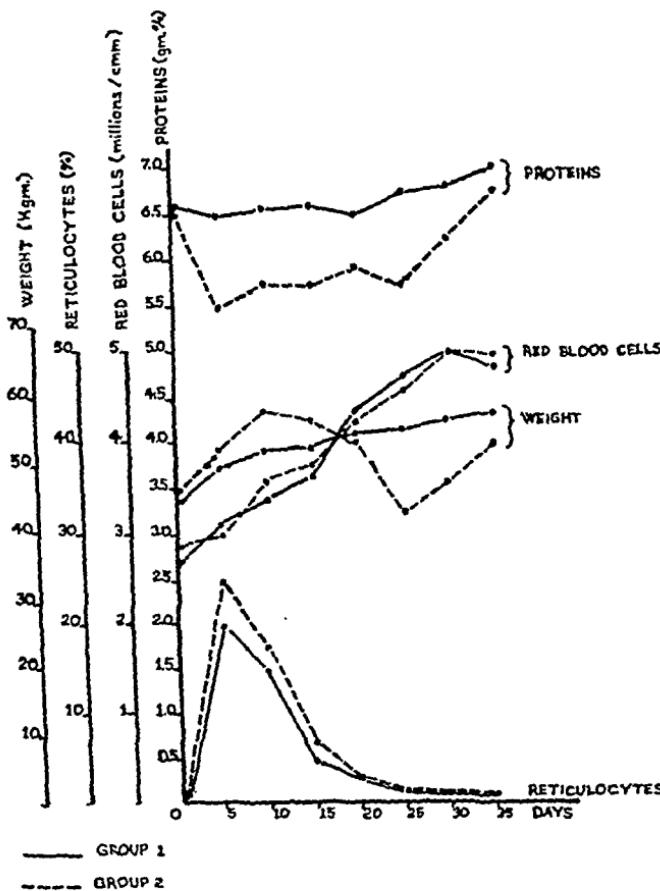


FIG. 1. RELATIONSHIP BETWEEN TOTAL SERUM PROTEIN LEVEL AND EDEMA IN PATIENTS WITH TROPICAL SPRUE UNDER THERAPY

The study includes 10 patients (group 1) in which edema rapidly improved and 10 cases (group 2) in which reticulocytes crisis and hematological improvement were accompanied by temporary generalization of the edema. Average figures, including red blood cells and reticulocyte counts are given for each group.

25 days after the beginning of treatment, together with a critical increase of the diuresis and a steady return of the serum protein level to normal values. Immediate improvement of the edema was obtained with plasma transfusion (250–300 cc. of lyophilized plasma) in five patients.

## DISCUSSION

The findings presented in this paper confirm the known fact that patients suffering from comparatively early sprue, in which edema is (in the experience of the writer) a minor and inconstant symptom usually present a normal total serum protein level; and they also give significant support to the theory of the hypoproteinemic pathogenesis of nutritional edema with the observation of the relationship between serum protein level and behavior of the edema during the stage of recovery of some cases of tropical sprue.

The report of the appearance of a "delayed" edema in previously "dry" patients recovering from different types of anemia or from malnutrition is not new. It has been observed in patients being treated for microcytic anemia<sup>7</sup>; macrocytic anemia<sup>3, 6</sup>; sprue treated with pteroylglutamic acid<sup>2</sup>; malnutrition<sup>9, 14</sup> and the enumeration is not assumed to be complete. As in the series of cases presented in the present paper, in most of these patients the appearance of edema has been related to a drop in blood protein level (particularly albumin fraction) noticed shortly after the beginning of treatment and its prompt regression has been usually obtained with plasma transfusions. In the particular case of tropical sprue, however, other factors besides hypoproteinemia may possibly cooperate to the temporary worsening of the edema during the stage of recovery of the disease. One of the most likely, at least in some cases, is represented by an improved absorption of  $\text{Na}^+$  and  $\text{Cl}^-$  ions, which may follow the reestablishment of a normal intestinal function under effective therapy (a deficient absorption of these ions is known to occur in some stages and cases of tropical sprue<sup>1</sup>). However, the close relationship between protein level of the serum and behavior of the edema and the response of the last to plasma transfusions show the primary role of hypoproteinemia.

It remains, of course, to be said that the pathogenesis of the remarkable drop of serum protein level in the early stages of recovery from an anemic condition is not very clear. It may be postulated that a greater demand of plastic material for active erythropoiesis from the blood forming organs would be responsible for a decrease in the plasma protein level, which would in turn cause appearance or extension of the edema. This theory, however, lacks experimental support and, even if suggestive, does not explain all findings in the series of patients presented in this paper. So, for instance, while one group of cases only presented temporary hypoproteinemia and subsequent extension of the edema during the stage of recovery from the disease, the writer was unable to find any statistically significant differences in severity of clinical symptoms and anemic condition between this group and the one whose edema responded favourably to treatment from the very beginning, and in which a drop in protein level of the serum did not occur.

## SUMMARY

Moderate edema with a normal total serum protein level were found in 10% of the patients in a series of cases of tropical sprue. In 45% of them a marked extension of the edema occurred during the first days of treatment, in direct relationship with the occurrence of the reticulocyte crisis and a noticeable drop in the total serum protein level. Regression of the edema occurred almost critically 20 to 25 days after the beginning of the treatment when the serum protein level began to rise steadily and could also be induced promptly by plasma transfusion. These observations suggest a direct relationship between hypoproteinemia and the temporary extension of the edema during the stage of recovery of some cases of tropical sprue and confirm its importance in the pathogenesis of nutritional edema. It is tentatively suggested that the drop of serum protein level in the first days of treatment may be caused by a greater request of plastic material for active erythropoiesis from the blood forming organs.

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## AN IMPROVED LIVER BIOPSY NEEDLE

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### INTRODUCTION

The conventional Vim-Silverman type liver biopsy needle is composed of two portions, an outer trocar and an inner split needle (Figure 1). In securing a biopsy of the liver, the outer trocar with the inner needle retracted, is thrust through the abdominal wall, often under peritoneoscopic guidance, until the point rests upon the liver capsule at the spot from which the biopsy is desired. The inner split portion is then advanced past the point of the trocar into the liver substance. The biopsy specimen is secured by holding the split needle in position within the liver parenchyma whilst the trocar is advanced, with a rotary motion, until it has passed the stationary tip of the split needle, whereupon the entire instrument is withdrawn and the contained biopsy tissue removed. The forward movement of the outer over the inner needle is usually limited by a setscrew or stop of some sort.

In practice, the most difficult detail of technique is holding the inner split needle at a constant point within the liver as the outer trocar is advanced over it, for when forward movement of the trocar is begun it is impossible to be certain that the inner needle is being held stationary. The fear of penetrating too deeply into the liver usually causes an unconscious withdrawal of the inner needle as the trocar is advanced over it. The result is usually an unsatisfactory biopsy specimen. Conversely if the impulse to withdraw the split needle is overcompensated the entire instrument may be thrust too deeply into the liver with consequent unnecessary risk of hemorrhage or damage to the organ.

The modification pictured in Figure 1 is designed to hold the inner split needle in a constant position during the advance of the outer trocar. It consists of a footpiece through which the outer trocar passes freely. A rigid guide parallel to the needle is attached to the footpiece. Sliding on the rigid guide, but capable of being fixed with a setscrew, is an arm to which is attached the external hub of the inner split needle.

In using the instrument, the trocar with the split needle sheathed within it, is advanced through the abdominal wall under peritoneoscopic control until the point rests upon the liver capsule. The footpiece is then dropped against the abdominal wall and the trocar and footpiece held firmly in relation to each other with the thumb and forefinger to prevent further advance of the trocar while the inner split needle is thrust into the liver substance. The setscrew of the crossarm is then tightened on the rigid guide which holds the split needle at

a constant point within the liver while the trocar is advanced through the foot-piece, with a rotary motion, until its forward progress is limited by the setcrew in the hub of the trocar. The entire instrument is then withdrawn and the biopsy removed.

Prior to use of the modification described, liver biopsy with the Vim-Silverman needle in our hands was not entirely satisfactory. It was often necessary to make two or even three punctures before an acceptable specimen was secured. Even then the biopsy was frequently composed of several small bits of tissue which were far from satisfactory to the pathologist. Others have reported similar experience. Since adopting the modification every biopsy has

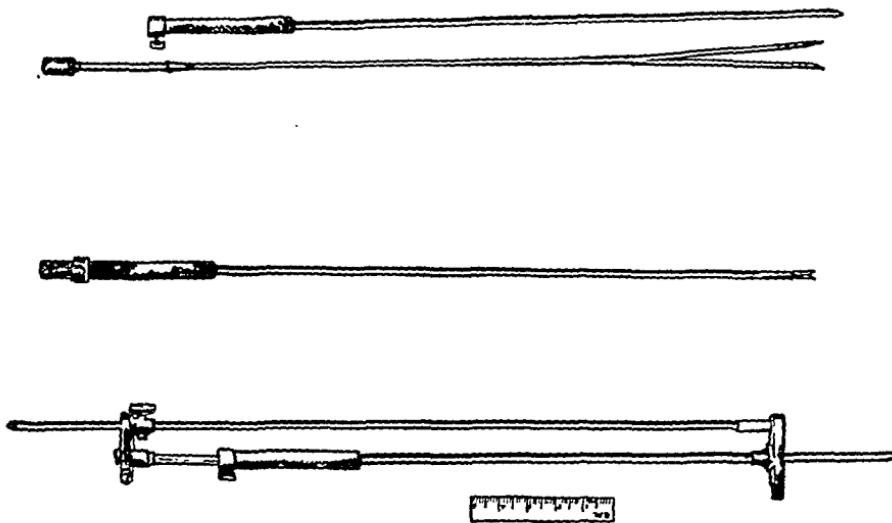


FIG. 1. Above, the two parts of Vim-Silverman needle; Center, conventional type needle assembled with inner split needle projecting past tip of trocar; Below, modification described as fitted to conventional type needle.

resulted in securing a uniform specimen from 2 to 2.5 cm. in length with a uniform caliber of 2 mm. As yet a second puncture has not been necessary nor has excessive bleeding been encountered. In addition, the knowledge that the inner split needle is always under perfect control lends confidence to the operator and removes a constant source of worry.

Experience has shown that when the anterior abdominal approach is utilized, the respiratory excursion of the liver is of small magnitude during normal breathing. It is therefore not necessary that the patient hold his breath during the period that the needle is within the liver substance. The procedure may thus be carried out in a leisurely and painstaking manner. Pentothal or other general anesthesia may be used if desired.

It is agreed among pathologists that the needle biopsy is preferable to tissue obtained by biopsy forceps during peritoneoscopy, for the latter often yields merely a biopsy of the capsule and gives but little information concerning the liver parenchyma. Since the improvement here described has been found to function so perfectly it was thought worth while to publish the technical details so that others might be encouraged to make more liberal use of the Vim-Silverman technique of liver biopsy.

## DIVERTICULA OF THE STOMACH; REPORT OF 26 NEW CASES\*

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### INTRODUCTION

The incidence of true diverticula of the stomach is sufficiently rare to be considered a clinical curiosity by various observers<sup>1, 2, 54</sup>. Martin<sup>2</sup> states that lack of experience in this rarity not only exists among clinicians but also among pathologists. Moses<sup>3</sup> reviewed 150 cases reported in the literature up to 1946. However, Bockus<sup>4</sup>, Shiflett<sup>5</sup>, and others, feel that many cases are not diagnosed because of a paucity of characteristic symptoms. Many authors<sup>1</sup> stress the questionable clinical significance of these lesions. Most of the literature on this subject is made up of articles that present one case and a review of the preceding literature. This has led to a confusing picture of the subject as well as recurrent evaluation of the very same cases.

### MATERIAL

Our interest in the subject was stimulated by a case seen in the Clinic of Michael Reese Hospital which presented features which have been neglected previously. The present report deals with 26 new cases of apparently true diverticula and 4 cases of false or acquired diverticula. Nineteen cases of true diverticula and 3 cases of false or acquired diverticula were gathered from the clinical records of the last 12 years at the Veterans Administration Hospital, Hines, Illinois. This institution had total admission during that period close to 130,000. In the clinical records of Michael Reese Hospital up to July, 1947, 4 cases were found, 2 more additional private cases were supplied by physicians of that institution, and another case of true diverticulum was seen by one of us (M. A. S.) while in military service in 1945.

### *History*

For those interested in the history of this entity, we refer to work of Lay Martin<sup>2</sup> who has published a creditable review of the earliest literature, and has unravelled many erroneous concepts as the original observations of this condition. Although the initial description of gastric diverticula has been traced to various writers as early as 1774, Helmout<sup>6</sup> was credited with the original clinical description in 1804.

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We are indebted to Drs. S. Portis, C. Lawrence and H. Arkin for use of their private cases. We also wish to express our sincere thanks to Dr. H. Necheles for his aid in preparing this manuscript.

However, Martin has found that the earliest authentic case was described by Thomas Baillie in 1793<sup>7</sup>. He further found that the original misconception as to Helmout's case stems from Voigtel<sup>8</sup> and that actually Voigtel claimed that Fournier was the first observer. This he also found to be error as the original case of Fournier<sup>9</sup> was that of a duodenal diverticulum and not a gastric one.

### *Incidence*

Feldman<sup>10</sup> found an autopsy incidence of approximately 0.02% and an incidence of 0.04% in 136,000 roentgen examinations of the stomach. This was confirmed by members of Mayo Clinic<sup>11</sup> who reported 0.02% in over 90,000 gastric roentgenological examinations and Reich<sup>12</sup> who found 0.03% in 19,022 gastric roentgenograms. However, Shiflett<sup>5</sup> reported an over-all incidence of 0.65 in 1937. In 768 roentgen examinations of the stomach and 887 of the colon, he found diverticula in the colon in 4.96% of the cases, in the duodenum in 3.74%; esophagus in 0.79; stomach 0.65%; and only one case of diverticulum in the jejunoleal region. Fraser<sup>13</sup> reported the same relative frequency of occurrence in the gastro-intestinal tract. Rigler<sup>14</sup> roughly approached this percentage in reporting 0.49% in 4,236 stomach examinations. It may be significant that the lowest percentage incidence is seen in larger series.

The estimated incidence of diverticula of the stomach at the Veterans Administration Hospital, Hines, Illinois, is approximately 0.015% of the total admissions and 2.6% of 350 gastroscopic examinations. Although it must be granted that this condition is relatively rare, the existence of such an entity must be remembered, especially in patients with otherwise undiagnosed gastrointestinal hemorrhage or with atypical gastrointestinal symptoms. The 150 cases reported in the literature might lead one to believe that diverticulum of the stomach is a clinical curiosity, but many more cases are probably being seen without ever reaching the literature, and an incidence of 0.015% of total hospital admissions should not be neglected.

### *Sex and age distribution*

The age and sex incidence of these lesions show a wide range in various reports. Age of predilection is usually given as from 30 to 50, but Reich's cases ranged from 36 to 71 years. In our series, the ages varied from 20 to 67 years in patients with true diverticula and from 29 to 73 years of age in the acquired. However, the source of material influences age distribution as well as sex incidence in any series; consequently our patients for the most part are males in the middle age groups, as they are veterans of either World War I or II. Rivers<sup>11</sup> youngest patient with a gastric diverticulum was 26, and 3 such cases were reported in children 7 years of age. A diverticulum was found in a fetus by Broman<sup>15</sup> while Pernkopf<sup>16</sup> and Sinclair<sup>50</sup> reported a diverticulum in a 4 month old infant. There is some question as to a female predominance with Feldman stating a 3:2 ratio, Bockus a 2:1 and Tracey<sup>17</sup> a 1:1.

### *Etiology*

Keith<sup>18</sup> pointed out that the stomach wall is weak at its junction with the esophagus, and the true diverticulum may develop here, which is the most common location

clinically. Bockus takes exception to Keith's theory, and does not believe it explains the etiology of diverticula at the cardia for, if this region is congenitally devoid of normal musculature, the incidence should be greater. Bockus proposes that the thinning out of the musculature found in the wall of many true diverticula is due to stretching of the pouch rather than congenital weakness. Alvarez<sup>19</sup> further disproved this theory by placing a balloon at this area in animals and exerting many times the normal pressure without producing diverticula. Fifty-six cases in Martin's series were examined histologically, and 16 had intact walls; 23 had thinned muscular layers; 6 had only mucosa and serosa; and in 8 the wall was not described. Hillemand<sup>20</sup> stated that gastric diverticula are common in hogs and monkeys but not in man.

Reich<sup>12</sup> theorized that constant pressure and irritation at the congenitally weakened area progresses to the formation of diverticula. As these diverticula become filled with food, repeated pressure distends the diverticular sac.

Resnick<sup>21</sup> noted that diverticula of the colon and duodenum are often observed together. He felt that diverticula are prone to occur at sites of incomplete peritoneal covering, such as appendices epiploicae of the colon, and at the cardia at the lesser curvature, where the peritoneum is reflected in the formation of the ileo-renal and gastro-splenic ligaments.

#### *Pathological classifications*

The pathological classification of this lesion has been under much discussion, but the consensus of opinion is that the diverticula should be separated into the congenital or true type, and the acquired or false. In the true diverticula there is no evidence of any organic disease as a causative factor. They are protrusions of the mucosa and submucosal layers herniated through a congenitally weakened muscular coat. The muscular coat of the diverticulum is usually absent according to Feldman,<sup>10</sup> but Rivers states all coats are outpouched. Usually they are located on the lesser curvature near the cardia on the posterior wall.

Martin subdivides gastric diverticula into pulsion and traction types. Pulsion diverticula are further subdivided into congenital, which are due to a muscle hiatus or local absence of gastric muscle, and muscle diastasis, which is a weak area distended by intragastric pressure.

The acquired, false or traction type is usually found near the pylorus, and less frequently in the body of the stomach. These are always secondary to some other disease process, either infectious or neoplastic, located in the gastric wall or outside, producing traction on the wall.

Feldman<sup>10</sup> briefly discussed three other possible types of diverticula. Transient diverticula are supposedly functional, and are usually found at the cardia in middle aged or old women. DeQuervain<sup>22</sup> reported two cases. A second type was diverticula of tumors, especially benign ones, and two cases of myoma with degeneration of the central portion producing pouching were described by Rowlands<sup>23</sup>. Sandstrom<sup>24</sup> reported one case in an adenoma. Trauma may occasionally produce a diverticulum.

Brdiczka<sup>25</sup> found 7 cases of pseudo diverticula of the greater curvature of the antrum

due to perigastric adhesions. Jordon and Lahey<sup>26</sup>, and Speese and Skillern<sup>27</sup> found that the so-called traction diverticula may be simple penetrating ulcers which produce a perigastritis with resulting diverticula. Tilger<sup>23</sup> described a traction diverticulum at the pylorus, caused by gall bladder adhesions.

Clinically, the type of diverticulum is relatively unimportant, as the clinician is only concerned with how much of the existing symptomatology is due to the diverticulum. We agree with Frank's<sup>28</sup> opinion, and consider all diverticula located at the cardiac end of the stomach as true or congenital as long as no other disease process is present that may produce a gastric outpouching.

#### ANATOMIC LOCATION

Akerlund<sup>29</sup> points out that congenital diverticula more commonly occur in the cardia on the posterior wall of the lesser curvature just below the cardioesophageal opening, while the acquired are more often near the pylorus. Feldman<sup>10</sup> found 85% of the diverticula at that location in the cardia. Rivers<sup>11</sup> however, found an entirely different type of distribution in his 14 cases with 43% at the cardia, 43% at the pylorus and 14% at the antrum. Tracey<sup>17</sup> in 35 cases, found diverticula of the cardia in 27 cases, pylorus 3, anterior wall 4, and posterior wall one. Ravenel<sup>30</sup> reported one case on the anterior wall. In summary of 103 cases, Martin found 61% within a radius of a few centimeters of the cardia. Thirty-nine per cent occurred along the lesser curvature. Occasionally, these lesions have been reported on the greater curvature on the anterior or posterior surface of the fundus.

In our series, the radiological location of true diverticula are listed in Table 2. Seventeen of 26 cases were located on the posterior wall of the lesser curvature of the cardia, while 7 were found at the same location in the pars media. Two diverticula were noted on the greater curvature of the cardia. Of the false or acquired diverticula, 3 were found in the pyloric region on the lesser curvature, and 1 was found at the posterior wall of the greater curvature in the pars media. Two of the 3 pyloric diverticula were on the posterior wall, and the third was on the anterior.

#### SIZE

The size of the diverticula found by Rivers was from 1 to 7.5 cm. in length, and Feldman stated that the range in size was from 5 to 40 mm. in diameter. The only specimen obtained in our series was circular and measured 7 cm. in diameter and 4.0 cm. in length; yet, on radiographic examination, this diverticulum was so large that it was mistaken for a cascade stomach (Figure 2). This discrepancy may be due to the fact that the diverticulum contracts markedly after surgical extirpation, while on x-ray it is distended by the weight of the barium mixture. The hiatus of the pouch varies considerably in size and the smaller the ostia the greater the retention in the sac.

## DIAGNOSIS

The symptoms and signs of diverticulum of the stomach are not characteristic, and the diagnosis cannot be made without the aid of roentgenograms and gastroscopy. Reinecke<sup>31</sup> states that classification of types of symptoms is untenable due to the great variation, and physical findings are no more consistent. Rivers<sup>11</sup> found that only 5 of his 14 cases had symptoms caused directly by the diverticulum. Both Martin<sup>2</sup> and Reich<sup>12</sup> reported about 64% of their surveyed cases to be asymptomatic, but Walters<sup>32</sup> reported that all 5 of his patients had definite symptoms of epigastric fullness and dyspepsia. All 26 of our cases have had symptoms referable to the gastrointestinal tract at one time or another, but 15 have had associated pathology that probably contributed to the symptomatology. The most commonly listed symptoms in the literature confirm those noted in our cases in Table 2. The epigastric pain can either be relieved or aggravated by food, and may radiate into the lower retrosternal region. Vomiting, belching, tenderness, dysphagia and occasional abdominal distention are also noted. Gastrointestinal bleeding is not a rare complication, according to Martin<sup>2</sup>, and the consensus of opinion is that it is due to stagnation in the sac, producing trauma by the food particles and the retention of an acid gastric content. Melena was noted in 5 of our cases and hematemesis in 3. Retention of food in the diverticulum may produce gasterospasm, and this coupled with the diverticular gastritis may, according to Walters<sup>32</sup>, account for pain.

The radiological diagnosis depends on the retention of opaque media, and is most commonly seen after the stomach empties. Almost all cases revealed retention after 6 hours. Lawson<sup>2</sup> reported retention of barium in 1 case for 24 hours; Geyman<sup>34</sup> for 48 hours; and Gray<sup>35</sup> found retention for 7 days. Retention was noted in 11 of our cases; for 36 hours in one (Fig. 2b); 24 hours in 5 (Fig. 4b); 6 hours in 3; and 3 hours in 2 cases. In an erect position a gas bubble and fluid level are frequently seen (Fig. 3b), but a lesion can also be missed in this position if the sac does not fill with gas. The best technic for completely filling the cardia consists of taking an erect, left oblique, recumbent, and Trendelenberg views. A diverticulum of the stomach was first noted on radiographic examination by Brown<sup>36</sup> in 1916, but he diagnosed it prior to surgery as a gastric ulcer. Akerlund<sup>29</sup> in 1923, laid down the essential requirements: 1) a mobile sac unattached to extragastric tissues, 2) a well defined, smooth shadow noted from various angles, 3) generally there is no tenderness. To these Reich added four more characteristics; demonstration of rugae in the mucosal lining of the neck, a characteristic location on the lesser curvature of the posterior wall of the cardia, retention of the barium from 6 to 24 hours, and the occasional ability to empty the sac by change of position.



8. EB	56	W/M	Epigastric pain Vomiting Bloating Epigastric pain Vomiting Nausea	Prox. pars media on post. wall. Retention 6 hrs. Post. portion of prox. part of lesser curv. at cardia, retention 24 hrs.	Post. wall near the lesser curv. of pars media —	Subacute chole- cystitis and choledochitis	Medical	3 admissions for recurrences of symptoms Symptoms prob- ably due to cholecystitis
9. JCD	24	W/M	Nausea	Diverticulum in the fundus	Post. wall at lesser curv. of cardia	Possible duodenal ulcer	Peptic ulcer diag- nosed 1-4 yrs. prior to present admission	Postop. x-ray failed to reveal diverticulum
10. CTS	37	W/M	Epigastric pain with periodicity Vomiting Loss of wt.	Proximal portion of the fundus	Fundus observed by sanguinous material, no os- tium visualized	—	Laparotomy—no diverticulum lo- cated. Small area of granula- tion tissue found and excised	—
11. KM	20	W/M	Hematemesis Weakness Dizziness	Less curv. border of the cardiac seg. Retention 6 hrs.	Large duodenal ulcer, penetrat- ing. Poor gall bladder filling	Medical	Resection of di- verticulum thru transthoracic ap- proach with in- version of stump	Postop x-ray negative. X- rays at first di- agnosed as es- ophageal stomach
12. JG	67	W/M	Bloating Periodic pain	Post. wall at cur- dia. Barium re- tained 6 hrs.	—	—	Diverticulum meas- ured 7 cm. x 4 cm. in thickness. Marked chronic inflammation.	—
13. FJW	52	W/M	Epigastric pain	—	—	—	Postop x-ray negative.	—

TABLE 1—Continued

CASE	AGE	RACE SEX	CLINICAL FINDINGS	X-RAY	GASTROSCOPIC FINDINGS	ASSOC. PATH.	TREATMENT	MISCELL.
14. MB	32	W/M	Epigastric pain with periodicity Tarry stools	Medial aspect of cardia of stomach	Post. wall of cardia near greater curvature	Duodenal ulcer	Medical	—
15. LK	40	W/M	Perumbilical pain Retention 6 hrs.	Medial aspect of cardia. Retention 6 hrs.	Post. wall of fundus	Duodenal diverticulum	—	—
16. NR	52	W/M	Vomiting Dysphagia Weakness Loss of wt.	Post. wall of cardia. Retention 24 hrs.	Post. wall of cardia. Inflamed containing food particles. Repeat—diverticulum no longer inflamed before surgery	Congenital right sided aortic arch	Invagination with purse-string type of suture	Daily lavage and medical treatment. Diverticulitis subsided. Post op x-ray diverticulum $\frac{1}{10}$ original size
17. EC			Case history not available		Lesser curv. of cardiac segment	—	Medical	—
18. JW	28	C/M	Vomiting and nausea	Possible diverticulum post wall upper $\frac{1}{2}$	Diverticular opening upper $\frac{1}{2}$ of post. wall	—	Medical	X-ray first diagnosed as cascade stomach
19. CB	23	C/M	Epigastric pain	Post. wall of cardia	Lesser curv. at cardia with mucous streaming over edge	Active duodenal ulcer	Medical	Gastroscopy unable to differentiate diverticulum from ulcer
20. IM	49	W/F	Belching Pain in left chest	Post wall of cardia	—	Diverticula of the colon	Medical	—

21. RB	48	W/M	Bloating Epig. pain Hematemesis	Cardia	Post. wall of cardia Hypertrophic gas- tritis	Medical	—
22. RB	48	W/F	Tenderness in epi- gastrium	Post. wall of lesser curv. Retention 3 hrs.	Diverticula recto sigmoid	Medical	—
23. NS	60	W/M	Halitosis Pyrosis Meteorism	Lesser curv. of cardia. Reten- tion 4 hrs.	—	Medical	—
24. MS	58	W/F	Fulness in throat Tenderness in epi- gastrium	Postero-medial wall at cardia	Atrophic gastritis. Ca. right breast	Medical	—
25.	64	W/F	Palpable mass Periodic pain Tarry stools	Pars media Post. wall.	Not seen	Duodenal ulcer	Medical
26. CC	52	C/M	Tenderness in epi- gastrium McIena 4 times Weakness	Tenderness in epi- gastrium Deformed duodenal bulb	Irregular depres- sion on post. wall of stomach near cardia on two occasions	Duodenal ulcer	Medical Seen by gastro- copy but not by x-ray



FIG. 1a

FIG. 1b

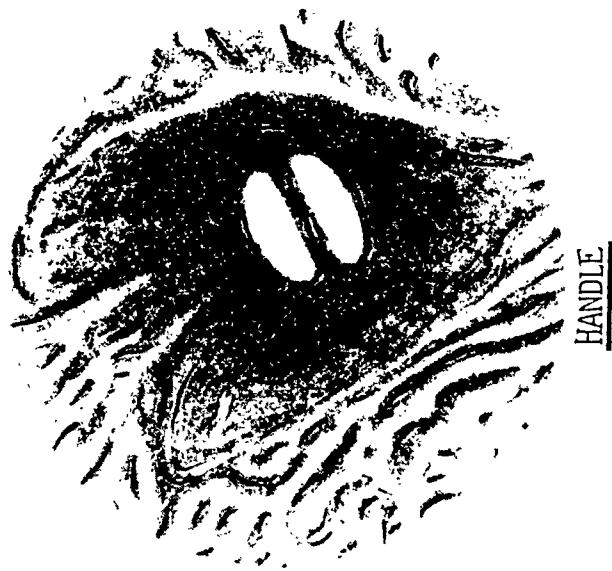


FIG. 1c

FIG. 1. Fifty-two year old white male with a history of vomiting and epigastric pain for four days:  
a) x-ray reveals large diverticulum posterior wall of the cardia at or near the esophageal hiatus,  
b) shows the sac as  $\frac{1}{6}$ th its original size three months after the sac was inverted by purse-string type  
of suture, c) artist's impression of gastroscopic picture as seen about one year after operation. Two  
orifices were seen separated by a thin fold of mucosa. The surrounding mucosa appeared slightly  
atrophic.

#### GASTROSCOPY

Gastroscopy may aid in the elimination of possibilities of other organic diseases, i.e. gastric ulcer. Whitehouse<sup>37</sup> feels that it can be done with compara-

tive safety and should precede surgery in all cases. Tracey<sup>17</sup>, however, feels that it involves possibility of perforation. He further states that during a gastroscopy, a capable surgeon should be on call in case of catastrophe. In our experience the visualization of the diverticular ostia by gastroscopy affords no more risk than any other gastroscopy. The gastroscopic picture as seen in 9 of our patients is so characteristic that it can easily be a valuable differentiation from other lesions which may confuse the radiographic picture. In 2 cases, gastroscopy revealed that suspected diverticula on x-ray were actually gastric ulcers, (Table 4, case 2), and (Table 3, case 2). Another case, seen by one of us (M. A. S.) in the service showed a large diverticulum-like pouch on the lesser curvature of the stomach that appeared to arise close to the cardia (Fig. 5b and Table 4, case 4). Several roentgenologists interpreted it as a diverticulum.

TABLE 2  
*Summary of 26 cases of congenital diverticulum*

CLINICAL FINDINGS	LOCATION ON X-RAY	LOCATION ON GASTROSCOPY	TREATMENT	ASSOCIATED PATHOLOGY	MISCELLANEOUS
Pain in epigastrium (18)	Post. wall of cardia (18)	Post. wall lesser curv. cardia (5)	Medical (21)	Duodenal ulcer (7)	A. Original x-ray diagnosis:
Vomiting (9)	Lesser curv. (16)	Pars media (2)	Surgical (5)	Diverticulosis coli (3)	1. gastric ulcer (2)
Bloating (6)	Greater curv. (2)	Post. wall greater curv. (2)	Not found (3)	Cholecystitis (2)	2. cascade stomach (2)
Weight loss (5)	Pars media (7)	Not seen (2)		Duodenal diverticulum (1)	B. Age
Tenderness in epigastrium (5)	Not seen (1)			Hypertrophic gastritis (1)	20-67 years
Melena (5)				Atrophic gastritis (1)	Average 49 years
Hematemesis (3)				Congenital right sided aortic arch	
Pyrosis (3)					
Weakness (3)					
Dysphagia (1)					

On gastroscopy a large crater covered with grayish white exudate was seen on the lesser curvature of the stomach near the cardia. This patient left the hospital contrary to medical advice and returned with a generalized peritonitis following perforation. Autopsy revealed a huge benign gastric ulcer. In the case to be reported in detail, this examination was able to follow the remission of an inflammatory process in the diverticulum prior to surgery. This inflammatory process was responsible for the symptoms and was detected only by gastroscopy. Another examination revealed a diverticular ostium in a patient on whom repeated radiological examinations were negative (Table 1, case 26). This may be explained by the presence of superficial gastritis or peridiverticular adhesions occluding the neck of the sac, thus preventing barium from filling the diverticulum. In two patients, gastroscopy failed to reveal the diverticulum seen on radiological study, and this was probably due to location. The



FIG. 2a



FIG. 2b



FIG. 2c

FIG. 2. Fifty-two year old white male who suddenly experienced sharp stabbing pain in the pit of his stomach one year ago. Pains have continued and radiated up to the sternum. This pain also aggravated by food, sitting or lying: a) illustrates a large diverticular sac which was diagnosed as a cascade stomach, b) barium is retained in the sac for 36 hours, c) the diverticulum was resected at a later admission and measured 7 cm. in diameter and 4 cm. in thickness. Microscopically, no muscle layers were seen, but the mucosa and submucosa were intact and showed only chronic inflammation. This case is discussed as Illustrative Case 2.

gastroscopic appearance is quite characteristic and cannot easily be confused with other lesions. We were never able to look into the sac of the diverticulum

and we would judge that because of the position of most diverticula this would be difficult to accomplish. Therefore, visualization consists of inspecting the ostium of the diverticulum. The depth of the opening is dark while in an ulcer crater the base is covered by exudate. The ostium may be perfectly round or oval and may change in size and shape during observation. In some cases a ridge or slight elevation is seen, suggestive of a ring of muscle fibres surrounding the opening. In other cases, rugal folds are seen radiating toward the ostium similarly to what one sees in a gastric ulcer. However, the fact that the base is not seen and the fact that the size and shape of the opening changes, dis-



FIG. 3a



FIG. 3b

FIG. 3. Forty-five year old white male complaining of pain in the epigastrium, pyrosis and frequent vomiting: a) demonstrates the typical mushroom sac with the small neck, b) shows the same lesion no longer filled with barium but filled with air, c) in an erect view the lesion was not seen. This lesion was seen on the posterior wall of the greater curvature at the cardia on gastroscopy. It was filled with greenish-gray material.

tinguishes it from an ulcer. When the diverticulum is large and retains food particles, the fluid mixture may be seen exuding from the ostium. When the ostium is large it may simulate in appearance a spasm of the body of the stomach or be suggestive of the antrum or an enterostomy stoma. The location and the history would of course, not necessitate this differential diagnosis.

In addition to verifying the presence of a diverticulum, gastroscopy will reveal the character of the surrounding mucosa. In this manner the factors causing the symptoms may be found. It is conceivable that ulceration in the region of the ostium and bleeding from the ostium may be seen.

Schindler<sup>8</sup> reported 3 cases of diverticula seen through the gastroscope, 2 of which were in syphilitics. He describes the picture as revealing a round, sharp

TABLE 3  
*False or acquired diverticula of the stomach*

CASE	AGE	RACE SEX	CLINICAL FINDINGS	X-RAY	GASTROSCOPIC FINDINGS	ASSOCIATED PA- THOLOGY	TREATMENT	MISCELLANEOUS
1. CC	44	W/M	Sharp pain lower abdomen Anemia Malnutrition	Greater curvature in pars media. No retention	—	TRB for advanced calculi of pancreatic duct. Pancreatic cyst	Laparotomy for pancreatic cyst	At autopsy diverticulum from post. wall of stomach 8 mm. in length pointing to pancreatic cyst, but not connecting
2. WG	29	W/M	Perumbilical pain	Filling defect in pyloric portion with diverticulum of antero-medial portion of stomach	Carcinoma of body of stomach	Gastric ulcer	4 Laparotomies and gastric resection	Extensive ulcer of posterior wall of stomach on lesser curv. at site of previous operation with many perigastric adhesions
3. LW			Soreness in epigastrium Vomiting	Large diverticulum lesser curv. in pyloric segment	Duodenal ulcer and bronchogenic carcinoma	Duodenal ulcer	Medical	
4. WMCK			Pain in epigastrium Tenderness in epigastrium	Pyloric antrum	—	Cholecystitis	Gastric resection	Chronic penetrating duodenal ulcer with 0.7 cm. out pouching in mucosa on anterior surface of pylorus

TABLE 4  
*Erroneous diagnosis of diverticula of the stomach*

CASE	AGE	RACE SEX	CLINICAL FINDINGS	X-RAY	GASTROSCOPIC	TREATMENT	MISCELLANEOUS
					—	Subtotal gastric resection	Extensive induration of posterior wall of stomach adherent to the pancreas. Chronic penetrating pyloric ulcer penetrating into pancreas. Fluoroscopy 3 wks. later ulcer found and much smaller than previous lesion
1. RS	53	W/M	Periodic epigastric pain Vague mass in epigastrium	Large gastric diverticulum in medial portion of stomach and overlies pyloric segment. Impr.; ca. of stomach with acquired diverticulum	—	Medical	Penetrating ulcer on lesser curv. just below cardia
2. JJD	35	W/M	Steady epigastric pain Pyrosis	Diverticular extension in upper portion of greater curv. on the ant. lateral aspect, mucosal pattern normal. Impr.; congenital gastric diverticulum	Depression about 1 cm. in diameter with grayish-green material, rugal folds converging toward it. Impr.; 1) superficial gastritis 2) benign gastric ulcer	Subtotal gastric resection	Penetrating ulcer on lesser curv. just below cardia
3. AAM	46	W/M	Severe epigastric pain Hematemesis Melena	3 x-rays series done about 2 yrs. apart, 2 diagnosed as penetrating ulcer on lesser curv. of cardia. The other series diagnosed as acquired diverticulum	—	Medical	Patient returned with peritonitis and died.
4.	50	W/M	Epigastric pain Melena	X-rays diagnosed as gastric diverticulum posterior wall, lesser curv. at the cardia by several radiologists	Benign gastric ulcer	Patient left hospital against medical advice	Autopsy revealed a perforated gastric ulcer

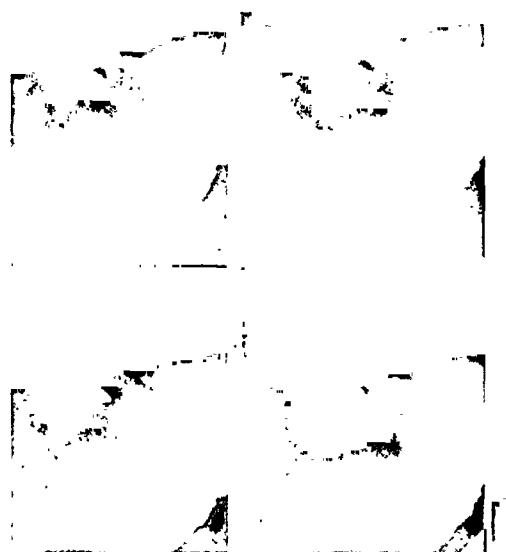


FIG. 4a



FIG. 4b

FIG. 4. Sixty year old white male complaining of abdominal pain, vomiting and tarry stools: a) polygrams demonstrate a small deposit of retained barium at the cardia which represents the diverticulum, b) barium is still retained at 24 hours. This patient responded to medical regimen.

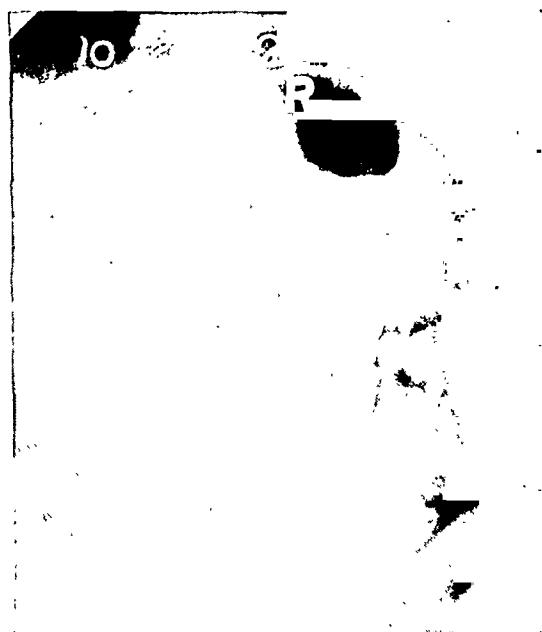


FIG. 5a



FIG. 5b

FIG. 5. a) Forty-six year old white male who had three admissions to the hospital for gastric ulcer; a large accessory pocket extending from the lesser curvature of the upper pars media; diagnosed as an acquired gastric diverticulum due to an old penetrating ulcer, with some barium retention in the pocket. Two years later a subtotal gastrectomy with a Hofmeister modification of a posterior polya anastomosis was done. A 2 cm. ulcer was seen with no evidence of malignancy or a diverticulum. b) Fifty year old white male with symptoms of epigastric pain and melena. Several radiologists reported this lesion as a gastric diverticulum arising from lesser curvature of the posterior wall at the cardia. Gastroscopy indicated a benign gastric ulcer. Patient perforated some time later and autopsy revealed a perforated benign ulcer.

opening with a diameter of the ostium smaller than the greatest diameter of the sac. The rugae around the opening were normal. If it is possible to reflect light into the diverticulum, it is seen to be covered by smooth, orange-red mucous membrane. The question as to whether syphilitic diverticula exist and whether they can be differentiated from congenital diverticula must be decided by further observation. In none of our cases was a clinical diagnosis of syphilis made. Beutel<sup>39</sup>, Pendergrass<sup>40</sup>, Heiniken<sup>52</sup> and Brown and Priestley<sup>46</sup> have reported cases in which gastroscopy was of value. Walters<sup>32</sup> in 1 case, failed to



FIG. 6. The gastroscopic picture of a 32 year old white male with 7 year history of recurrent duodenal ulcer, showing a large diverticular ostia on the posterior wall near the greater curvature just below the cardio-esophageal junction. The greater curvature is seen on profile to the right and mucosal folds are shown radiating into the ostium.

visualize the diverticulum by means of gastroscopy, but in a previous report Schmidt and Walters<sup>51</sup> described the diverticular ostia seen gastroscopically in 2 cases. Figure 6 shows an artist's impression of the gastroscopic picture of the diverticular ostium seen on patient number 14 in Table 1.

#### DIFFERENTIAL DIAGNOSIS

Bockus differentiates diverticula from benign or carcinomatous ulcers by location, as peptic or malignant ulceration is rarely near the cardia. The ulcer niche rarely changes its size, it is tender, and has a broad base; an accessory

pocket of the perforated ulcer is often separated from the lumen by a fistulous tract. A diverticulum has a narrow base in relation to the size of the pouch, has a rather characteristic mushroom or oval shape, and the contour of the marginal silhouette may change on films taken in different positions. Templeton<sup>41</sup> differentiates the cascade type of stomach by the absence of a true stalk and variation in size. We were impressed with the retention of barium in the diverticular sac. If barium remains in the sac after 6 hours, it is unlikely to be a cascade stomach. Diaphragmatic hernias enlarge with inspiration and thus differ from diverticula according to Pendergrass<sup>42</sup>. The original radiologic diagnosis in our series was of gastric ulcer in 2 cases and cascade stomach in 2 cases, and diagnosed 2 (Table 4) prepyloric penetrating ulcers as acquired diverticula, and an ulcer of the lesser curvature as a congenital diverticulum.

#### ASSOCIATED PATHOLOGY

Reich<sup>12</sup> found associated gastrointestinal disease in 30% of his cases. We found a much higher rate, approaching 60%. Of the three cases reported by Chavarri<sup>55</sup>, one had a concomitant ulcer of the lesser curvature of the stomach and another had a neoplasm of the lower third of the esophagus. The co-existence with tumors, benign or malignant, is rare according to Feldman<sup>10</sup>. The x-ray demonstration of this would be difficult, for growth occurs in the region of the neck of the sac, thus obstructing it, the diverticulum is not visible radiographically. If the tumor is small and located at the base or at the margins of the neck, and irregularity to the otherwise smooth pouch would be noted and this should be suggestive of carcinoma. Mayo<sup>42</sup> and Mellon<sup>43</sup> report such cases. Associated lesions found by Tracey<sup>17</sup> were: duodenal ulcer in 7; carcinoma of the stomach in 3; cholelithiasis in 2; and diverticulosis coli in 2. Other conditions reported are syphilitic ulceration, hiatus hernia, and heterotopic pancreatic tissue. Eusterman and Balfour<sup>54</sup> have reported concomitant diverticula of the duodenum and colon in 12% of the cases. The associated pathology in our series is listed in Table 2. Falconer and Geyman<sup>34</sup> found pancreatic tissue in a diverticulum at the pylorus. There have been 14 such cases reported, but only one was located at the cardia, according to Martin<sup>2</sup>. He also noted that adenomyoma in a diverticulum was seen in 4 cases, carcinoma in 3, and fibrosarcoma in 1. Love<sup>45</sup> reported a case of a large gastric diverticulum on the greater curvature near the pylorus within which there was an ulcer.

#### COMPLICATIONS

The numerous complications associated with diverticula of the colon do not affect the stomach, according to Reich<sup>12</sup>. This may be attributed in the main to good blood supply at the cardia, mobility and activity of the stomach as a

whole, and the relatively lower content of bacteria in that organ. Thus, injection of the general peritoneal cavity from the thinning of the diverticula wall without perforation does not occur, nor does chronic local peritonitis. Gangrene, due to strangulation or closure of the neck by edema or congestion, has not been reported. Herniation through the abdominal wall or the diaphragm by the diverticular sac has never been seen. The lodgement of food masses and associated acute inflammation of the diverticulum was not noted by Reich, but a few cases have been reported by Maissa<sup>45</sup>. Feldman<sup>10</sup> lists the radiographic sign of diverticulitis as tenderness over the sac, irregularity of the contour, narrowing of the hiatus, fixation of the pouch, mucosal changes in the pouch. Albrecht<sup>49</sup> emphasizes the sign of tenderness as being pathognomonic. The inflammation may spread producing a peridiverticulitis with subsequent adhesion to the adjacent organs. Both the lodgement of food and the associated diverticulitis were seen gastroscopically by us in Case I. The complication of hemorrhage has been discussed under symptoms. Brown and Priestly<sup>46</sup> have reported a case in which recurrent hemorrhages from a gastric diverticulum have occurred.

#### *Illustrative case I*

This 52 year old white male was first admitted to Michael Reese Hospital on 12-27-45, complaining of loss of strength in his arms, stiffness in his legs, inability to eat because of choking sensation and loss of 20 pounds in the last 8 months. Patient stated that up until 30 days prior to admission he was perfectly well, but then developed cramping sensation in both hands with weakness, forcing him to quit work as a sewing machine operator. For the last 4 days he had been unable to eat solid food and vomited everything but fluids. His past history revealed appendectomy and cholecystectomy done 25 years ago, and an episode of glycosuria which was not treated. At one time he had a BMR of plus 28, and was treated by Lugol's solution. Family history was negative. Physical examination revealed a poorly developed, poorly nourished white male, nervous and apprehensive but not acutely ill. Physical findings were negative except for 1 plus occult blood in the stools on one occasion. X-ray showed a large diverticulum arising from the posterior wall of the cardia at or near the esophageal hiatus (Fig. 1a). An incidental finding on chest films was a right-sided aortic arch. After 2 weeks he was discharged as asymptomatic. In November, 1946, he had recurrence of symptoms and entered the Veterans Administration Hospital, Hines, Illinois, where he was gastroscoped on 2 occasions. On the first examination a large diverticulum of the posterior wall of the cardia was seen, the ostium and surrounding mucosa were greatly inflamed and sac contained much greenish material as well as food. He received a bland diet and gastric lavage. After a month he was re-gastroscoped and the diverticular opening was still present but it was no longer inflamed nor did it contain food. His symptoms subsided and he gained weight. He was then referred to surgery to prevent recurrent divertic-

ulitis. A left subdiaphragmatic approach was done but the surgeon had difficulty in locating the diverticulum and opened the stomach to locate the ostium. Because of the difficulty in mobilizing the sac, the diverticulum was closed off by simple invagination with a purse-string type of suture. No malignancy was found at operation, and the patient's post-operative course was uneventful and he was discharged improved.

He was next seen in the gastro-intestinal section of Mandel Clinic, Michael Reese Hospital, three months later, complaining of pain in the abdomen for the past two weeks. This was described as pressure in the region of the incision and under the sternum. Radiological examination revealed the diverticulum to be still present but about  $\frac{1}{6}$  of its original size (Fig. 1b). He was treated conservatively and studies by the neurological clinic as well as the orthopedic clinic failed to find the cause of his weakness and tremor. In 3 months, patient had gained 5 pounds and no longer complained of abdominal discomfort.

The patient returned to the Veterans Hospital in January 1948 complaining again of nausea and vomiting of several weeks duration. This attack followed an episode of chills and fever due to an atypical pneumonia. Gastric reontgenograms revealed the diverticula to be still present and the same size reported on his last examination. Gastroscopy was again done, but this time instead of one ostium of the diverticulum, two orifices were seen separated by a thin fold of mucosa. This lesion was located directly on the posterior wall of the cardia, and the immediately surrounding mucosa was not inflamed but in fact, was slightly atrophic (Fig. 1c). The patient responded to the medical management of his pneumonia and was discharged feeling better. It is felt that the diverticulum was entirely asymptomatic at this admission.

### *Illustrative case II*

This 52 year old white male complained of belching after eating certain foods and a full feeling in the epigastrium for many years. This was never accompanied by pain. About July, 1943, there was a rather abrupt onset of sharp, steady epigastric pain radiating to both upper quadrants and to the mid-chest. Pain tended to occur after meals, lasting from 15 to 45 minutes, and was usually relieved by milk. There was no nausea or vomiting. A local physician diagnosed a peptic ulcer and put him on a diet, which somewhat relieved him for about one month. He discontinued the diet and had no further trouble until May 1946. During the next three months the trouble recurred intermittently and was essentially the same as in 1943. In August, the pain became quite severe, and was of a sharp, steady nature, not relieved by milk as previously.

He was admitted to the Veterans Administration Hospital, Hines, Ill., in August 1946. He was first considered to have a peptic ulcer and was put on an ulcer regime. The gastrointestinal work-up was negative except for the radiological report of a cascade type of stomach (Fig 2a). He did not respond to the ulcer management and was discharged as having a functional gastrointestinal disease.

Pains have persisted since this initial discharge and radiated from the pit of the stomach up to the sternum and mid-chest. This pain no longer bore a food-ease

relationship, and was frequently aggravated by eating. It also would last from 10 to 12 hours at a time, and occasionally would awaken him from sleep. This pain would usually occur when the patient was sitting or lying down. There was a loss of 26 pounds in weight during the course of the year, and the patient was readmitted to the hospital in March 1947.

The patient was a thin, white male appearing chronically ill. His heart was enlarged to the left and he had a blood pressure of 220/120. Tenderness was elicited below the xyphoid cartilage. The genito-urinary consultant found a chronic prostatitis and urethral stricture. An electrocardiogram revealed a non-specific abnormal pattern with left ventricular strain. Roentgenography revealed a large congenital diverticulum on the posterior wall at the cardia, with retention of the barium in the sac for 36 hours (Fig. 2b). On review of the old x-rays, the previously reported cascade stomach was in reality the same diverticulum.

A resection of the diverticulum was done thru a transthoracic approach with excision of the sac and inversion of the stump. On gross examination, the diverticulum was circular and measured 7 cm. in diameter and 4 cm. in length, and the microscopic report was of marked chronic inflammatory changes, but no malignancy. Mucosa and submucosa were intact, but no muscle layers were seen.

The immediate post-operative course was uneventful except for a thrombo-phlebitis which required bilateral ligation of the anterior femoral veins. Repeat gastro-intestinal x-ray showed no evidence of the diverticulum and the patient was discharged completely asymptomatic.

#### TREATMENT

Before attempting to treat this condition, it is important to determine whether one is dealing with a single uncomplicated diverticulum or whether it is inflamed, retentive and the cause of the existing symptoms. *Because of the frequency with which gastric diverticula may be asymptomatic, their mere presence should not be accepted as the sole factor accounting for the patient's symptoms.* Associated lesions such as malignancy, or benign tumors, peptic ulcer, or gastritis must be excluded. If the symptoms are mild, a medical regimen of bland, smooth diet, alkalies and bismuth 1-2 hours after meals will bring relief. Gastric lavage and postural drainage may be helpful when retention in the diverticulum is present. However, if the symptoms persist or associated lesions such as benign or malignant ulcerations are found, surgery is indicated. Total excision of the diverticulum with inversion of the stump should be attempted. Simple invagination of the pouch with closure of the mural muscular ring by purse-string type suture as recommended by Ferguson and Cameron<sup>56</sup> is not adequate as seen in the recurrence, in Illustrative Case I, of the diverticulum following this type of procedure. Reinecke<sup>31</sup> attempts to rationalize why the diverticulum is often missed at surgery by suggesting the possibility of a very small orifice among the coarse mucosal folds. Furthermore, the fundus of the

stomach, especially the cardiac orifice, is comparatively inaccessible surgically. Walters<sup>32</sup> states that to obtain the best exposure one may have to divide the gastrolienal ligament and the gastrocolic omentum, thus permitting mobilization of the fundal end downward and toward the mid-line. Occasionally, the gastrohepatic omentum must also be divided. This difficulty in visualization of the diverticulum at surgery is seen in 5 of our cases in which 3 diverticula could not be located. Thus, it becomes apparent that the failure of the surgeon to find the diverticular sac does not necessarily indicate a mistaken diagnosis.

Bell and Golden<sup>47</sup> believed that postural drainage with medical regimen should be tried in all cases where the diverticulum occurs at the cardia. In those cases where the lesion is in the lower  $\frac{2}{3}$  of the stomach, surgery should be done because of possible associated malignancy and the frequent mistaken radiographic diagnosis of diverticula in that region.

#### DISCUSSION

Our incidence of 0.015% of all admissions leaves this entity in the group of infrequent medical conditions. However, if we compare the number of patients with diverticula with the total number of admissions for gastrointestinal complaints or look at our incidence in gastroscopic examinations of 2.6%, it becomes a relatively important cause for gastrointestinal symptoms.

Its importance to the internist and gastroenterologist lies in its diagnostic difficulties. Symptoms are neither diagnostic nor characteristic but it should be kept in mind that it can be productive of symptoms and should be thought of in the differential diagnosis of upper gastrointestinal complaints. It is likely that the production of symptoms depends upon complications such as inflammation or ulceration of the diverticulum and both of these may depend on retention of food particles in the sac.

Diverticulum should be thought of as a cause for upper gastrointestinal hemorrhage as was found in several of our cases. If the hemorrhage is extensive and surgery indicated, it is important to locate the sac as, even when demonstrated preoperatively, the surgeon may not be able to find it.

A gastric diverticulum may also cause typical ulcer pain, relieved by food and alkalis. This happened in one of our cases (Table 1, case 13). The only atypical feature was that the pain was located high in the xiphoid region. The patient's response to ulcer management was so spectacular that a clinical diagnosis of ulcer was made in spite of negative roentgenographic reports. The diagnosis came under suspicion when the pain returned about three weeks later, and did not respond to an ulcer regimen. The sac of the diverticulum was missed on the first x-ray series, because it was so large and thought to be a cascade stomach. Extirpation of the diverticulum resulted in complete relief of symptoms.

Another symptom complex we observed was nausea, vomiting, and loss of weight, which led us to think of a gastric malignancy. Retention of food particles and inflammation of the stomach wall surrounding the diverticulum and undoubtedly the wall of the diverticulum seemed to have caused symptoms. Bland diet, gastric lavage, and postural drainage resulted in marked clinical improvement.

#### SUMMARY AND CONCLUSIONS

1. Twenty-six cases of true and 4 cases of false gastric diverticula are reported. They may not be as rare as believed generally.
2. Nine of eleven cases of the true diverticula were visualized gastroscopically, the others were not gastrospected. One of the true diverticula visualized on gastroscopy was not seen on roentgenograms and this was probably due to superficial gastritis or peridiverticular adhesions occluding the sac at the time of the barium meal.
3. Gastric diverticula may produce incapacitating symptoms, among them pain, vomiting, and hemorrhage.
4. Diagnosis in this condition may be difficult unless the entity is kept in mind and careful roentgenographic and gastroscopic studies are done.
5. Medical therapy consisting of bland diet, lavage, postural drainage and antispasmodics may be effective.
6. Surgical extirpation may be needed to prevent recurring symptoms.

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## THE RESPONSE OF HUMAN INTESTINAL MOTILITY TO TETRAETHYL AMMONIUM CHLORIDE

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### INTRODUCTION

Tetraethyl ammonium chloride, a quaternary ammonium compound which is structurally related to acetylcholine, has been shown to block effectively the transmission of impulses across the ganglia of the autonomic nervous system<sup>1-3</sup>. Reports concerning the effect of this drug on the gastro-intestinal tract are relatively meager<sup>4-6</sup>.

Holt and his co-workers<sup>5</sup>, employing a roentgenographic technic, observed that tetraethyl ammonium chloride produced a prompt decrease in gastric tone, dilatation of the stomach and an inhibition of gastric peristalsis after its parenteral administration. A few marginal fibrillations were seen after injection of the drug. A profound inhibition of peristalsis and of rhythmic contractions of the small intestine was noted. No appreciable change in the haustral pattern of the colon was observed, although it was noted that during the period in which the drug exerted its effect, the colon could be markedly distended without the production of a defecational impulse. The duration of the activity of the drug varied from "a few minutes" after intravenous injection to three hours after intramuscular administration. It was found, however, that the drug produced no relaxation in instances of cardiospasm. The normal esophagus was likewise unaffected by the preparation. These investigators, therefore, concluded that tetraethyl ammonium chloride had no direct musculotropic effect.

Chapman, Stanbury and Jones<sup>6</sup> employed a tandem balloon, kymographic technic to study the effects of tetraethyl ammonium chloride on the duodenum and jejunum of 8 subjects. They found a suppression of tone and motility within 30 to 120 seconds after the intravenous injection of the drug in the majority of instances. There was a partial return of tone in 30 to 55 minutes and a partial return of motility in 20 to 43 minutes. During the period of effect of the drug there was no change in the threshold of pain that resulted from distending a balloon in the intestine, although 2 patients with intestinal pain were relieved by the preparation. These observers suggested that tetraethyl ammonium chloride possibly exerts an effect on the myenteric plexus or the intestinal musculature in addition to its autonomic blocking effect.

Studies of the effect of tetraethyl ammonium chloride on gastric motility and secretory function have been reported in an earlier paper<sup>7</sup>. The present communication concerns itself with the results of our studies on the motility of the intestinal tract following the administration of this drug. For the sake of brevity, tetraethyl ammonium chloride will hereafter be referred to as TEAC.

#### MATERIAL AND TECHNIC

These investigations were made on 4 subjects who volunteered their services for the study of the effects of TEAC. The first patient had undergone ileostomy and transverse colostomy after excision of the terminal part of the ileum, cecum, ascending colon and a portion of the transverse colon for fat necrosis of the mesentery complicating hemorrhagic pancreatitis. The second subject had undergone loop colostomy of the descending colon because of an abscess which had complicated osteomyelitis of the hip and which had extended into the rectum. The third and fourth subjects had undergone colostomy on the descending colon following combined resection for carcinoma of the rectum.

The apparatus employed in this study has been described in detail elsewhere<sup>8</sup>. Medication was withheld for at least six hours preceding the studies. The investigations were carried out one hour after a light breakfast. The patients were placed supine on a comfortable cot. In the first subject, a single balloon made of condom rubber was placed in the ileac stoma and another in the transverse colic stoma. In the other 3 subjects the limb of the descending colon proximal to the colic stoma was intubated by an apparatus that contained two such balloons in tandem. These balloons were connected to water-air reservoirs. Through sidearm connections, the balloons were distended with 15 cc. of water. Continuity was established between the balloons and the water-air reservoirs, and the pressures were allowed to equalize. The final hydrostatic pressure was approximately 18 cm. The final volume of each balloon was approximately 22 cc. The water-air reservoirs were connected to optical manometers which allowed the fluctuations in pressure exerted by the intestine upon the balloons to be recorded photographically, thus providing a permanent and continuous recording. Respiratory excursions were damped out by adapters inserted into the connecting tubing. Control observations were carried out for 30 to 45 minutes prior to administering TEAC. The drug was given in varying amounts by intravenous injection in all instances. The recordings were continued until recovery from the action of the drug was apparent.

#### RESULTS

Table 1 summarizes the effects observed following the intravenous administration of TEAC to 4 subjects. After a latent period of  $\frac{1}{2}$  to 3 minutes, in-

intestinal motility was abolished in all instances. There was a good deal of individual variation in the duration of the abolition of motility. In subject 1 (fig. 1) the motility of the small intestine was abolished for 50 minutes and the motility of the colon was abolished for 65 minutes after the intravenous injection of 200 mg. of TEAC, while the colon of subject 2 remained quiescent for only 31 minutes after a similar injection. In subject 3 (fig. 2) colonic activity was abolished for 22 minutes after injection of 300 mg. of TEAC, while in subject 4 complete inhibition of colonic motility continued for 57 minutes after administration of 400 mg. of the drug. Upon recovery, the intestines of subjects 1 and 3 showed activity greater than that present before administration of TEAC, the colon of subject 2 showed an unaltered motility, while the colon of subject 4 was less active than during the control period.

TABLE 1

*Effects of tetrathyl ammonium chloride on intestinal motility in 4 human subjects*

SUBJECT	AGE	SEX	SEGMENT STUDIED	TEAC	LATENT PERIOD	MOTILITY ABOLISHED	TONE
	years			mg.	minutes	minutes	
1	47	F	Ileum	200	1	50	Slightly depressed
			Transverse colon	200	1	65	Slightly depressed
2	32	M	Descending colon	200	1	31	Slightly depressed
3	60	M	Descending colon	300	3	22	Depressed*
4	57	M	Descending colon	400	½	57	No effect

\* Fibrillary contractions, lasting 3 minutes, occurred in this subject.

Intestinal tonus was depressed in subject 3, less so in subjects 1 and 2, and none at all in the fourth subject. With recovery, the tonus returned to control levels.

It is interesting that subject 3 (fig. 2a) demonstrated apparent fibrillary contractions of the intestinal musculature, which occurred at a rate of 24 per minute, immediately after TEAC had been given, lasting 3 minutes. The subject was not aware that these fasciculations were taking place. This effect was not apparent in the other 3 subjects. It is quite doubtful that this apparent fibrillation was due to respiratory excursions; the subject was breathing at a rate of 16 times per minute and, as previously indicated, respiratory excursions were damped out of the recordings by adapters inserted into the connecting tubing.

#### COMMENT

In a previous report<sup>7</sup>, it was shown that the intravenous injection of 400 mg. of TEAC inhibited the motor function of the human stomach for periods of 35 to 43 minutes in 4 subjects. The present investigation has, in 2 instances,

a unanimity of opinion among investigators that the myenteric nerve plexuses are of primary importance in the mediation of co-ordinated impulses essential to the propulsive forms of peristalsis, there is much divergence of opinion as to whether rhythmic contractions are neurogenic or myogenic in origin. Bayliss and Starling<sup>10</sup> held to the myogenic view, since the contractions were observed to persist after the application of nicotine to the excised intestine. Alvarez<sup>11</sup> is of the same opinion. Cannon<sup>12</sup> expressed the thought that the rhythmic contractions were essentially myogenic in nature but were under the control of "local motor centers" of the myenteric plexus. As Evans<sup>13</sup> has pointed out, there is good evidence that smooth muscle, such as is present in the intestinal tract, is inherently rhythmic. However, the regular contractions obtained after functional denervation by nicotine differ from those previously observed, in that they are smaller, more regular and show no fluctuations in tone, amplitude or complexity<sup>13-15</sup>. Berkson<sup>14</sup> stated that the intrinsic nerve plexuses give rise to impulses which act as a regulating force for the muscular beatings, although they do not originate the movements. On the other hand, Thomas and Kuntz<sup>15</sup> concluded from their studies that the inherent myogenic contractions would be entirely inadequate functionally in the absence of nervous control. Yanase<sup>16,17</sup> found, in guinea pig embryos and later in human fetuses, that no intestinal activity took place until after the development of the myenteric plexus and its connection with the longitudinal muscle layer of the bowel wall. He concluded that intestinal motility is neurogenic in origin.

Since TEAC blocks impulses traversing autonomic ganglia and since the intestinal innervation is derived from the autonomic nervous system, one would naturally expect traveling peristaltic contractions to be abolished by the drug, as indeed they are. However, one observes that all forms of activity, including the rhythmic contractions, disappear after injection of TEAC. TEAC has not been observed to have a direct inhibitory myotropic action<sup>5</sup>. Indeed, preliminary studies by one of us (H. S. B.) have indicated that the drug may actually have a direct stimulatory effect on the isolated intestinal musculature of the guinea pig, which likely explains the fibrillation reported by Holt and co-workers<sup>5</sup> and observed in the previous investigation<sup>7</sup> and in subject 3 of this study. These facts lead us to feel that the rhythmic contractions of the intestinal tract are principally neurogenic in origin. Definite conclusions in this regard cannot be drawn until further definitive investigations have been carried out.

#### SUMMARY AND CONCLUSIONS

1. Tetraethyl ammonium chloride administered intravenously promptly inhibited the motor functions of the intestine in 4 human subjects.

2. There seem to be wide variations in individual responses to the drug.
3. It appears that the motility of the intestinal tract is inhibited by tetraethylammonium chloride for a longer period than is the motility of the stomach.
4. There is some reason to feel that the rhythmic intestinal contractions are principally neurogenic in origin.

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## THE INCIDENCE OF CHOLELITHIASIS IN THE NEGRO AS COMPARED WITH THE WHITE

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### INTRODUCTION

This study concerns itself with the comparative incidence of cholelithiasis in the negro and white races as revealed by a survey of the available case histories in the Charity Hospital in New Orleans from 1906 through July 1st, 1937. Thereafter, through July 1st, 1947, data were obtained directly from the hospital's cross files. No attempt was made to classify the type or site of stone formation. The patient's age, sex, history of antecedent infections, pregnancies and the imponderable factor of racial admixture were outside the scope of this study. Proof of the existence of gall stones was on the basis of radiological, surgical or autopsy recognition.

### FINDINGS

The following data were obtained.

1) Hospital admissions (1906-July 1, 1947)—1,409,632	
White—738,271 (52.4%)	
Negro—671,361 (47.6%).	
2) Number of cases of Cholelithiasis (1906-July 1, 1947)—1538	
	<i>Per cent of total cases</i>
White—1188 (77.3%)	0.16%
Negro—350 (22.8%)	0.05%
	<i>Per cent of total admissions</i>

As a check on the above figures, all of the acute cases admitted to the hospital with a diagnosis of gall stone "colic" for a five year period from 1936 through 1941 were investigated. The total was 364 or 73.62% white and 86 or 26.38% negro. The reasoning here was that the negro might through unavailability of medical care or indifference to the same carry his stones in silence—only presenting himself for aid in the acute phase. If such were the case, biliary colic would be the final common denominator for both white and colored. The above ratio, however, tends to corroborate the preceding figures with the much lower incidence of cholelithiasis in the negro as compared with the white.

The possibility of a higher "pain threshold" in the negro can but be conjectured. That, too, is beyond the scope of this study.

### DISCUSSION

The application of the idea of stasis of bile secretion as it concerns the inception of gall stones, is particularly interesting when associated with diet and

specifically the "high fat" content of the average negro's diet. The older generation of negroes were by nature and circumstance preponderantly fat eaters. This observation results from the fairly intimate contact that any practitioner in the south has with his negro patients' eating habits.

One may safely state that the negroes' staples in the past consisted of such food items as side meat (preponderately fat), turnip greens, cowpeas, corn meal and molasses. In addition, turnip greens and the side meat are usually cooked together for two hours or more and there is a resultant "pot likker", in itself most palatable and nutritious and at the same time representing a readily assimilable liquid high in fat content. This diet varied little from day to day and for that matter from meal to meal. The end result was a duodenal mucosa bathed at regular intervals with the fat stimuli necessary for the secretion of the hormone cholecystokinin. If this hypothesis is correct there resulted little chance for the negro's bile to become static. The past tense is used in reference to the negro's diet because, as in all of his habits, transition is taking place in what he eats. As they continue to adopt the more complex diet of the white race, a similar survey of the Charity Hospital case records will be interesting two generations hence.

Rodman<sup>1</sup> stated that during fifteen years of surgery at the Louisville (Kentucky) City Hospital there was no record of cholelithiasis clinically or at autopsy in a negro and only one in ten years of surgery in Philadelphia. Mitchell<sup>2</sup> noted that in a series of 1600 autopsies only fifty presented cholelithiasis, eighty five of these 1600 being male negroes with no stone and thirty seven female negroes with two gall stones found. Mosher<sup>3</sup> in 1655 routine autopsies found gall stones in 34 of the 634 negroes or 5.5% and eighty in the 1018 whites or 7.8%. Lieber<sup>4</sup> in 20,451 autopsies (13,038 white, 7,913 negro) done at the Philadelphia General Hospital revealed that 2,226 had gall stones. Of these 1832 or an incidence of 13.3% occurred in the whites, and 394 or an incidence of 4.98% in the negroes. Bloch<sup>5</sup> and Boland<sup>6</sup> have both noted the low incidence in cholelithiasis in the negro, the former from a perusal of Charity Hospital records in the past.

The medical literature has revealed scant but interesting statistics, with equally vague opinions, as to the low incidence of cholelithiasis in the negro. His posture, supposed comparative freedom from constipation (which I find debatable), simplicity of diet, life of manual labor, stronger abdominal musculature, ease of carrying and bearing children in the case of the female and other commonplace speculations have been brought forward.

Naunyn's idea of infection would seem to have little basis as applied to the negro, since they have their share of infected prostates and vesicles, tubes and ovaries, tonsils, carious teeth, intestinal parasites, systemic diseases such as syphilis and the like.

I have given thought to the existence of some anatomical differences between the structures of the biliary system in white and colored, but Trotter<sup>7</sup> is of the opinion that none exist. The rather well known fact that diseases connected with cholesterol metabolism such as gall stones, arteriosclerosis, and xanthomatosis are scarce in the Oriental, since the Oriental diet is largely exempt from animal protein as noted by Snapper<sup>8</sup>, tends to confuse the issue. As suggested by Ivy<sup>9</sup> the Oriental gall bladder may empty better in response to fats. On the other hand since cholesterol is the component part of the larger percentage of gall stones, some argument is lent to the stasis theory in that no matter how high the cholesterol "titer" in the body metabolism may be, the negro limits its formation into gall stones by ready evacuation of the biliary system.

#### SUMMARY

A survey of the case histories at Charity Hospital, New Orleans, from the year 1906 through July 1, 1947, revealed 52% White and 47% Negro admissions. There were disclosed 1538 authenticated cases of cholelithiasis during the same period and, of this number, 23% were Negro and 77% were White. It is conjectured that the marked lower incidence in the Negro has been due to the high fat content of his diet.

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## NEEDLE BIOPSY OF THE LIVER\*†

### II. EXPERIENCES WITH MALIGNANT NEOPLASM

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During the past 4 years, needle biopsy of the liver has been performed 357 times on 308 patients at the Cincinnati General Hospital without a serious complication. A description of some of our experiences and the technique used has been reported<sup>1</sup>. All but nine of the biopsies were performed with the Vim-Silverman needle; the remaining ones being done with the technique of Rohholm and Iversen. Opportunity has been afforded to perform liver biopsy on 53 patients with malignant neoplasm of the liver, the diagnosis being verified by necropsy in 27 instances, by operation in 6, and by biopsy in the remaining 20. The primary tumor sites are listed in Table I.

The liver biopsy showed the presence of neoplasm in 41 of the 53 cases. Tumor was not detected in 12 biopsies in 5 of which no liver tissue was obtained. The inadequate biopsies were performed early in the course of our experience when only one attempt was made to obtain a specimen. The remaining 7 samples in which hepatic substance was obtained showed biliary cirrhosis in 1, cholangitis and bile stasis in 2, portal cirrhosis in 1, and normal liver in 3. Among the 41 patients whose biopsies were positive for neoplasm, 5 required 2 and 1 required 3 biopsies to demonstrate the presence of tumor. (It is our practice, whenever necessary, to perform repeated biopsies in order to confirm or exclude the presence of neoplasm of the liver.)

The 41 biopsies designated as positive yielded specimens containing unequivocal neoplasm. Table II indicates the histologic nature of the lesions studied. The histologic patterns seen in the various biopsies were of the usual varieties obtained by less specialized methods. The hepatomas (Fig. 1) were characteristic, exhibiting interlacing cords of polyhedral cells mimicking those of normal liver and often showing intracytoplasmic bile production. Those lesions termed "probable cholangiomas" were, of course, not distinguishable from well differentiated metastatic adenocarcinoma (Fig. 2) issuing from the pancreas or extrahepatic bile ducts. Despite atypism they maintained resemblance to biliary ductules by reason of relatively orderly acinus formation,

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‡ Fellow Of The National Cancer Institute.

TABLE I

*Primary site of tumor in malignant neoplasm of the liver (53 cases)*

	NUMBER OF CASES
Site undetermined.....	15
Liver.....	11
Pancreas.....	8
Lung.....	6
Stomach.....	6
Eye (melanosarcoma) .....	2
Colon.....	2
Cervix.....	1
Breast.....	1
Retroperitoneal sarcoma.....	1

TABLE II

*Histologic nature of the lesions studied in the biopsy specimens (41 cases)*

	NUMBER OF CASES
Hepatoma.....	4
Adenocarcinoma, probable cholangioma.....	4
Metastatic carcinoma, unclassified.....	9
Metastatic oat cell carcinoma.....	6
Metastatic adenocarcinoma.....	12
Metastatic colloid adenocarcinoma.....	3
Anaplastic neoplasm.....	1
Metastatic melanoma.....	2

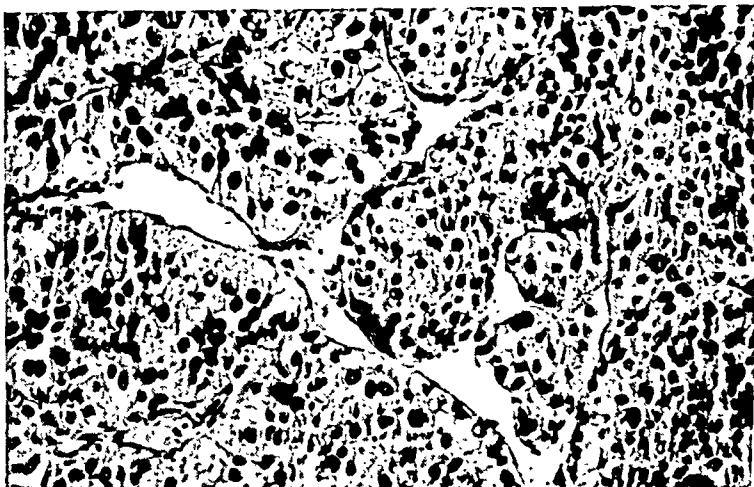


FIG. 1. (J. R. Case #222403) HEPATOMA

Bulbous cord-like masses of neoplastic hepatic epithelium border upon sinusoid-like crevices. Although evident in the slide, bile droplets do not appear in the illustration.

fairly characteristic mucin production and, even in the small biopsy, multicentric distribution. In the cases of metastatic melanoma (Fig. 3), the cytologic features and heavy melanin deposit were unmistakable. The majority of the tumors encountered were nondescript in structure (Fig. 4) falling into the categories of adenocarcinoma and medullary, or scirrhous carcinoma. The initial sites of these could not be predicted with certainty. In 3 instances the

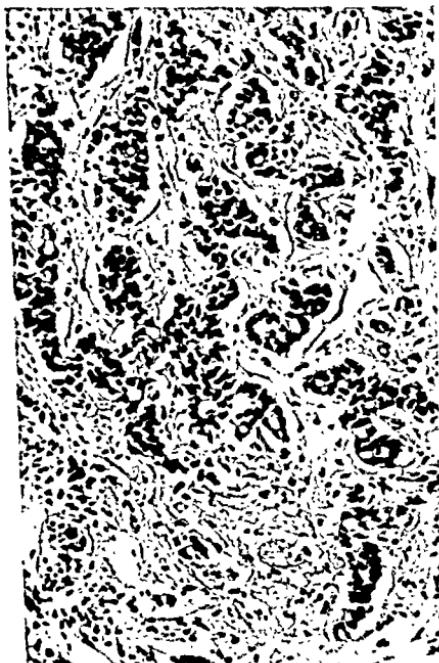


FIG. 2

FIG. 2. (F. N. Case #195129) CHOLANGIOMA

The tumor exhibits a scirrhouss quality. Tongues of neoplastic cells show lumen formation and mimic proliferating biliary ductules.

FIG. 3. (W. S. Case #206643) METASTATIC MALIGNANT MELANOMA FROM THE EYE

Interlacing nests of melanoma cells appear. Interspersed are many pigment deposits appearing black in reproduction.

presence of mucin (Fig. 5) indicated origin in the gastrointestinal tract and the carcinoma differed in no manner from that usually seen in that system. The tumors classified as oat cell carcinomas (Fig. 6) were so identified on the basis of clusters of small, closely packed epithelial elements with scanty cytoplasm and ovoid dark staining nuclei. In each instance a primary lung tumor was demonstrated. The lesion listed as anaplastic tumor appeared as small groups of primitive neoplastic elements scattered among liver structures or lying within vascular channels (Fig. 7).

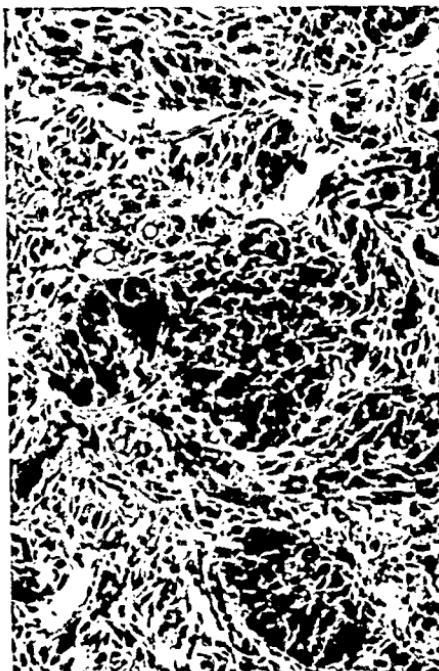


FIG. 3

Of the 41 patients with positive biopsies, the clinical impression of malignancy (not necessarily hepatic) was confirmed in 32 patients by the biopsy. Among the remaining 9 patients, in only one of whom neoplasm was suspected clinically, biopsy done to explain the cause of hepatomegaly resulted in the establishment of a correct diagnosis (Table III). The contribution of liver biopsy to the diagnosis of malignant neoplasm of the liver is indicated in Table IV.

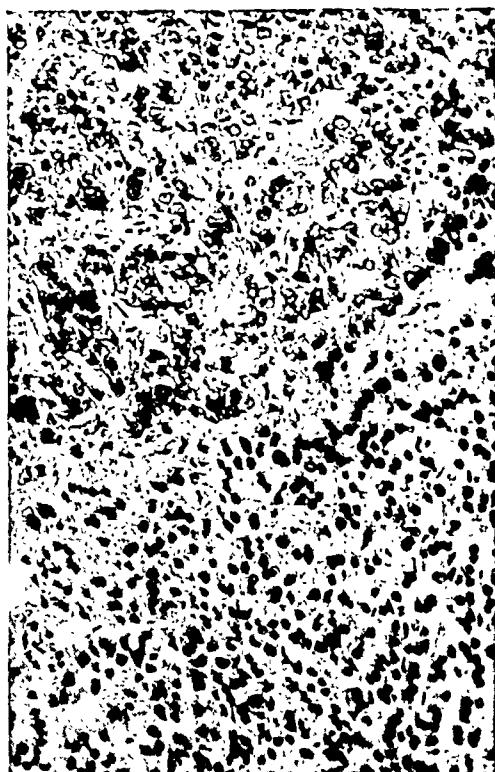


FIG. 4

FIG. 4. (E. S. Case #229046) A NODULE OF METASTATIC CARCINOMA OF GLANDULAR CHARACTER  
The tumor contrasts sharply with adjacent parenchyma.

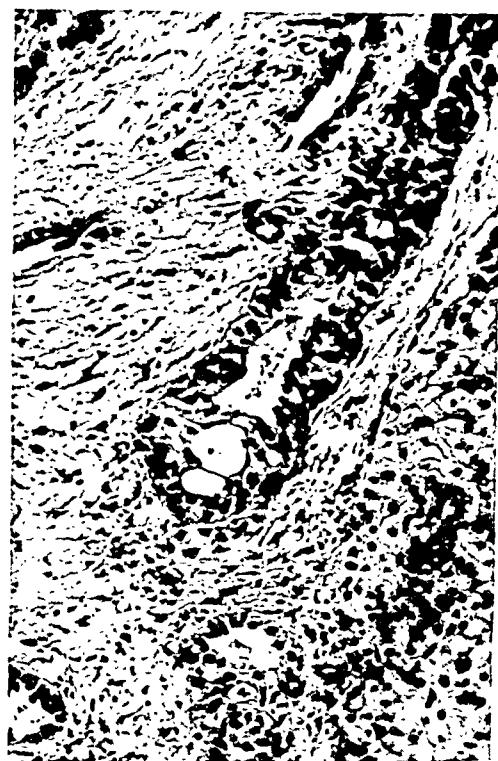


FIG. 5

FIG. 5. (S. B. Case #222217) METASTATIC ADENOCARCINOMA FROM THE COLON  
Neoplastic acini contain abundant mucin secretion.

Among the 7 cases in which biopsy, though satisfactory, failed to reveal the neoplastic process, either operation or necropsy demonstrated wide-spread intrahepatic tumor in 4 cases and sparse involvement in 3.\* Similar follow-up on the 5 cases in which the biopsy was a technical failure revealed wide-spread intrahepatic tumor in 4 and an unknown degree of involvement in 1. On the other hand, in 41 cases in which positive biopsy had been obtained a widely

\* In 1 case of carcinoma of the stomach neoplastic involvement of the liver was by direct extension only and was limited to the left lobe.

disseminated process was present in 19, scant evidence of metastasis in 1, and an undetermined degree of dissemination in 21. Thus, although the number of unsuccessful biopsies in which adequate tissue was obtained is small, it seems reasonable to conclude that the probability of obtaining neoplastic cells in the biopsy specimen is related directly to the extent of the intrahepatic spread of the tumor.

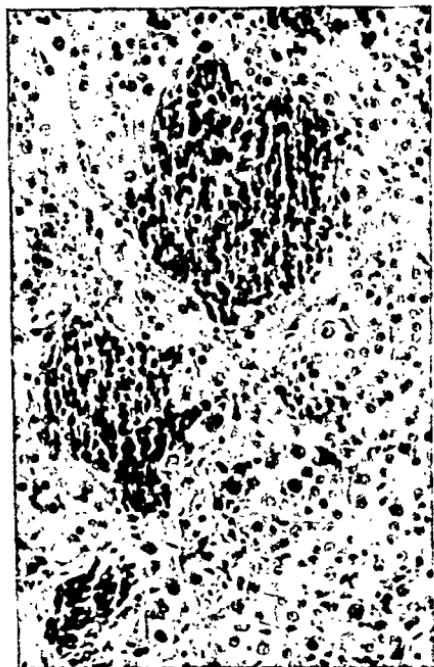


FIG. 6

FIG. 6. (P. O. Case #203384) INTRALOBULAR MASSES OF METASTATIC OAT CELL CARCINOMA ARISING IN THE LUNG

Liver cells, though displaced, remain intact and there is neither inflammatory nor desmoplastic reaction.

FIG. 7. (E. D. Case #226791) ANAPLASTIC CARCINOMA

The section shows normal liver structure. Within a perilobular lymphatic several small clusters of undifferentiated tumor cells appear.

Of the 53 patients, all but 2 had enlarged livers on physical examination. 33 of the patients presented nodular livers on palpation, in 8 of whom the hepatic tumor was primary. The needle biopsy revealed neoplasm in 26 of these 33, no neoplasm in 2, and inadequate specimens in 5. Among the 33 cases, a positive diagnosis was obtained in 18 of 23 with the lateral approach and 8 of 10 with the anterior approach. 18 patients had smooth livers to palpation, in 15 of whom biopsy revealed malignancy. The biopsy was done



FIG. 7

through a lateral transpleural approach in 16 of these patients and through an anterior approach in the remaining 2.

In the course of concomitant clinical studies, a variety of laboratory tests were conducted. Among these, a surprisingly large number of positive reactions to the cephalin cholesterol flocculation test were encountered. An attempt to correlate the histologic character of the liver with this test met with no consistent results. In only 31 cases in which the procedure was carried out, did the biopsy sample contain liver parenchyma in addition to the tumor and in 12 of these the amount of liver substance was quite small. Among the

TABLE III  
*Cases in which results of liver biopsy changed the clinical diagnosis*

CLINICAL DIAGNOSIS	BIOPSY DIAGNOSIS
1. (a) Cirrhosis (b) Possible sprue	Metastatic adenocarcinoma
2. Pneumonia	Metastatic bronchogenic carcinoma
3. Cirrhosis	Hepatoma
4. Cirrhosis	Hepatoma and cirrhosis
5. Hepatoma	Metastatic adenocarcinoma
6. Amoebic hepatitis	Metastatic colloid adenocarcinoma
7. Possible cirrhosis, sulfadiazine sensitivity	Hepatoma
8. Hepatomegaly, cause undetermined	Metastatic neoplasm, unclassified, with necrosis
9. Infectious hepatitis	Metastatic adenocarcinoma

TABLE IV  
*Value of liver biopsy in the diagnosis of malignant neoplasm of the liver (53 cases)*

	NUMBER OF CASES
Confirmed the clinical diagnosis.....	32
Revealed the correct diagnosis.....	9
Failed to demonstrate neoplasm.....	7
Biopsy specimen inadequate.....	5

19 cases with adequate liver tissue, 5 showed both parenchymatous damage and positive flocculation tests and seven normal parenchyma with negative tests. In the remaining 7, however, 4 cases with liver disease had negative tests and three cases with normal liver had positive tests. Among the 12 cases with minute pieces of liver, 7 had tests correlating with the histologic status (2 positive and 5 negative). However, in this group there were also 4 apparent false positive tests and 1 false negative. These findings would seem to indicate that the cephalin cholesterol flocculation is not fundamentally a test of liver function.

Neoplastic involvement of the liver is notoriously elusive to clinical examination and even to surgical exploration. The yield of positive results (77%) obtained in this study was unexpectedly high. Although the level of successful biopsies may well fall as our experience with this method broadens there is nevertheless every reason to consider the procedure of needle biopsy as an important adjunct in the clinical investigation of cases of this nature.

#### SUMMARY

1. Using the lateral (transthoracic) approach in 41 patients and the anterior approach in 12, the presence of hepatic neoplasm was revealed by means of needle biopsy in 41 of 53 patients with either primary or secondary neoplasm of the liver. In five of the twelve failures the biopsy specimen was inadequate for examination while in seven the specimen removed, though adequate, did not contain recognizable tumor tissue.

2. The biopsy confirmed the clinical impression of malignancy in 32 of the 41 cases. In the remaining nine cases, in eight of which malignancy was not suspected clinically, the biopsy changed an incorrect to a correct clinical diagnosis.

3. The frequency of a positive diagnosis was not significantly greater in the 33 cases in which the liver was palpated as nodular than in the 18 cases in which the liver was palpated as smooth. Among the 33 cases with nodular livers, it is of interest that a positive diagnosis was obtained in 18 of 23 with use of the lateral approach and 8 of 10 with use of the anterior approach.

4. A surprising number of positive cephalin cholesterol flocculation tests were encountered in the course of the study. Consistent correlation with the histologic status of the liver parenchyma, as revealed in the biopsy specimens, was lacking.

We wish to thank Drs. William E. Molle and Harold H. Steinberg for help with the earlier biopsies included in this study.

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## THE ABSORPTION, DESTRUCTION, AND EXCRETION OF ORALLY ADMINISTERED THIAMIN BY HUMAN SUBJECTS\*

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Contrary to the accepted idea that thiamin is readily absorbed<sup>1-2</sup>, the data in the literature indicate definite limitations to human intestinal absorption of this important vitamin. This is indeed surprising, for thiamin, a normal and necessary constituent of all micro-organisms and plant and animal tissues, is rapidly diffusible through artificial membranes; like dextrose, it is readily phosphorylated in the body and in the form of diphosphothiamin plays a dominant role in metabolism. In fact, from the data at hand and from those we shall present in this paper, one may infer that the animal organism either has developed no special mechanisms for absorption, or even may have developed barrier mechanisms.

The small quantities of thiamin in the daily diet or small supplements of thiamin are apparently readily absorbed as indicated by the daily urinary excretion and its relation to the excretion after administration of test doses. Excretions of from 14 to about 50%, depending somewhat upon the level of intake of thiamin in the normal diet, have been reported<sup>3-10</sup>. An excretion of 20% or more is usually obtained when adequate diets are administered<sup>8-11</sup>. The following 4 examples indicate the relation between the daily level of excretion and the extra excretion after administration of small test doses:

(1) In the experiments of Oldham and associates<sup>11</sup>, 2 children excreted the following respective percentages at dietary levels of approximately 0.500, 0.600, 0.725 and 0.950 mg. thiamin per day: 12 and 14; 18 and 23; 23 and 20; 32 and 29. The recovery of single *oral* test doses at the same 4 dietary intakes were, respectively: 5 and 12; 22 and 32; 17 and 18; 22 and 29% in 24 hours.

(2) In experiments with 5 women in equilibrium with a diet of approximately 2000 calories containing 1.000 mg. of dietary and crystalline thiamin, Mason and Williams<sup>7</sup> recovered from 13.3 to 24.3, or an average of 20.5% in 24 hours; a single *intramuscular injection* of 1.00 mg. resulted in additional recoveries of 12.4 to 26.6, or an average of 19.1% in 24 hours. On further supplementation to a level of 2.000 mg. per day, recoveries of 37 to 43%, or an average of 39% were noted; a single *intramuscular injection* yielded recoveries of 19 to 52%, or an average of 39%.

(3) In an experiment with 3 men, maintained on a diet of 4,640 calories containing a total of 3.99 mg. of dietary and crystalline thiamin, Keys et al<sup>12</sup>

\* This investigation was aided by the Clara A. Abbott Fund of Northwestern University.

noted an average recovery of 24% in 24 hours; an *oral* test dose of 1.00 mg. yielded an average recovery of 17.3% in 24 hours.

(4) In an experiment with 5 men, at equilibrium with a diet of 3,400 calories containing 0.85 mg. dietary and 1.51 mg. crystalline thiamin, or a total of 2.36 mg., Friedemann and Ivy (unpublished data<sup>13</sup>) obtained recoveries of 14.6 to 22.9, or an average of 18.8% in 24 hours; from 21 to 27%, or an average of 25.2%\*, was recovered within a fasting period of 4 hours when 1.00 mg. was injected slowly *intravenously* at the end of the experiment.

Thus, in the 4 experiments cited, the excretion of thiamin at adequate levels of intake was approximately of the same order whether the vitamin was administered orally, intramuscularly<sup>3, 15</sup> or intravenously.

At higher levels of intake, the absorption, as indicated by urinary excretion, is not as complete and differs somewhat, depending upon the dose and method of administration. The 2 children studied by Oldham et al.<sup>11</sup> excreted 33 and 49% on a total daily intake of 4.80 mg., or approximately 1.6 mg. at each meal. With a single oral dose of 5 mg. given on successive days, Schultz, Light and Frey<sup>16</sup> obtained recoveries of 24 to 42%; on giving 10 mg., only 19 to 21% was recovered. Similar results were obtained by Youmans et al.<sup>17</sup>.† An average recovery of about 26% in 48 hours—about 14% within 24 hours—was noted by Melnick, Field and Robinson<sup>8</sup> after a single oral dose of 5 mg. Thus, the limit of absorption of a single oral dose appears to be about 5 mg.

However, this estimate is perhaps too high, since Schultz, Light and Frey<sup>16</sup> and Youmans et al.<sup>17</sup> found increased quantities of thiamin in the stools with single oral doses of 5 mg. With an additional quantity of 5 mg., almost all of the additional vitamin was recovered in the stool. According to Schultz, Light and Frey, the maximum single dose which can be absorbed completely is 2 to 3 mg.

Relatively little<sup>18</sup> or no measurable absorption<sup>19</sup> has been noted when the vitamin is given in retention enemas, which involves exposure of only a limited area of the colon. The most rapid excretion is noted within 3 to 8 hours after administration of a single does of 5 mg. with food<sup>8, 20</sup>, in spite of considerable residues of thiamin in the feces. Therefore, the absorption seems to be confined largely to the upper intestinal tract. In aged persons, the absorption is apparently extremely limited throughout the intestinal tract<sup>21</sup>.

The purpose of this paper will be to define the limits of absorption and destruction in the body of normal human subjects within therapeutic ranges of oral administration. In subsequent communications, it will be shown that thiamin in addition to limited intestinal absorption has a renal "threshold" at about 1 microgram per 100 cc. of plasma—the lowest of any known biologically

\* In confirmation of Najjar and Holt<sup>14</sup>, less than 1% of the injected thiamin was recovered in the subsequent 20 hours.

† Personal communication from Dr. John B. Youmans.

important compound—and that levels of more than 10 micrograms per cent the rate of excretion falls within the range of maximal renal clearance rates of such drugs as phenol red, diodrast and penicillin.

#### EXPERIMENTAL

The subjects were medical students and laboratory workers, varying in ages from 20 to 46 years. Since the conditions differed somewhat in each experiment, the pertinent details will be given in the discussion of results.

Urine was collected in 1 gallon amber glass jugs containing 5 cc. of 20 N H<sub>2</sub>SO<sub>4</sub>. This yielded an approximate acidity of 0.1 N in the 24-hour sample. At this acidity, bacterial growth was inhibited and no loss of thiamin was noted within 2 weeks when the samples were refrigerated. Each daily sample was either analyzed immediately or a one-tenth aliquot was transferred to a bottle containing a composite sample. The latter was kept in the deep-freeze unit until ready for analysis.

All stools were collected in tared containers which were kept in the deep-freeze unit. In experiments 1 and 2, individual samples were collected. In experiments 3 and 4, the stools were collected in one or more containers over periods of 4 or 5 days, or until the subject had at least 5 large bowel movements. The over-all interval of time was recorded, and from this the average daily excretion of thiamin in the feces was calculated. For example, at 9:30 a.m. on the first day, a subject had a bowel movement which was discarded; the sixth stool was collected at 4:00 p.m. on the fifth day. Therefore, the total interval was 126.5 hours. The method, although simple, is subject to some error, and this may account in part for the variations in the results. However, in our experience, it has yielded more consistent results than other procedures of collection in which markers of charcoal or dyes were used. All single samples were analyzed immediately, or, in the case of frozen composite samples, as soon as possible after the collection was completed.

Total thiamin was determined by the method of Jansen<sup>22</sup> as modified by Hennessy and Cerecedo<sup>23</sup> and Friedemann and Kmieciak<sup>24</sup>. Free thiamin was determined similarly, except that the digestion with taka-diastase was omitted.

#### RESULTS

##### *Oral administration of a single dose of 50 mg. thiamin*

*Experiments 1 and 2.* Two experiments were performed in which 50.0 cc. of a solution containing exactly 50 mg. of thiamin was given after the first meal of the experimental period. The first was undertaken with one subject, B. J., who was maintained on a weighed diet of 2,700 calories containing about 1.2 mg. thiamin and 70 gm. of protein per day. The second experiment was under-

taken with four subjects who received a diet of 2,800 calories containing approximately 2.0 mg. of thiamin and 104 gm. of protein per day. The difference of the levels of thiamin intake in the 2 experiments is indicated by the urinary excretion during control periods of 20 days which average 0.181 mg. thiamin per day in the first, and from 0.579 to 0.810 mg. thiamin per day in the second experiment.

Subject B. J. was constipated and had scanty, hard stools. He was unable to give a specimen on 2 of the 12 days of the experiment. The 4 subjects of

TABLE I

*Experiment 1. Oral administration of a single dose of 50.0 mg. thiamin*

Subject B. J. The calculated average daily excretions of thiamin during the last 6 days of the 20-day control period were as follows: urine, 0.181 mg.; feces, 0.249 mg. The results represent the net recovery after ingestion of the vitamin.

DAY OF EXPERIMENTAL PERIOD	NET RECOVERY OF THIAMIN		CALCULATIONS <i>mg. net thiamin</i>
	Urine	Feces	
	mg.	mg.	
1	4.58	0.02	Total ingested..... 50.00
2	3.81	0.15	Urine..... 12.59
3	0.93	0.15	Feces..... 24.35
4	1.28	0.02	Total recovered..... 36.94
5	0.33	*	Destroyed..... 13.06
6	0.33	0.42	
7	0.18	15.48	
8	0.34	6.23	
9	0.27	1.26	
10	0.25	0.29	
11	0.15	*	
12	0.14	0.34	

\* No bowel movement.

experiment 2 had normally appearing stools and at least 1 bowel movement each day. However, subject J. M. of the latter group experienced some difficulty in obtaining a daily stool sample.

Subject B. J. (Table I) excreted large quantities of urinary thiamin, 4.58 to 3.81 mg., on the first 2 days after ingestion of the solution containing 50 mg. of thiamin. He excreted somewhat less on the third and fourth days, 0.93 and 1.28 mg., and, thereafter, rapidly diminishing quantities. The excretion of thiamin continued above the basal level up to the twelfth day when the experiment was discontinued. This continued excretion above the basal level was due perhaps to large amounts absorbed during the first 2 days. It is

significant that the urinary excretion diminished rapidly *before* any of the vitamin was recovered in the stools.

Somewhat the same results were obtained in experiment 2 (Table II). Because of the high dietary intake of thiamin, the net daily urinary excretion could not be judged as accurately as in experiment 1. The greatest excretion occurred on the first 2 days; and regardless of the thiamin content of the feces, the excretion fell before all of the fecal thiamin was excreted.

In the case of B. J. (Table I), 12.6 mg. net were recovered in the urine, and 24.4 mg. net in the feces, or a total of 37 mg. In contrast to this, all of the

TABLE II

*Experiment 2. Oral administration of a single dose of 50.0 mg. thiamin*

The calculated average daily excretions of thiamin during the last 6 days of the 20-day control period, in the order of subjects from left to right, were: feces, 0.404, 0.436, 0.396, and 0.284 mg.; urine, 0.701, 0.702, 0.579, and 0.810. The subjects received 12 small rubber bands in gelatin capsules and 50.0 cc. of a solution containing exactly 50 mg. of the vitamin.

DAY OF EXPT.	H. N.			M. H.			J. H.			J. M.		
	Rubber bands	Thiamin		Rubber bands	Thiamin		Rubber bands	Thiamin		Rubber bands	Thiamin	
		Feces	Urine		Feces	Urine		Feces	Urine		Feces	Urine
1	5	36.50	1.63		0.25	2.46		0.14	1.94		0.12	2.65
2	7	3.30	1.03	9	31.10	1.24	1	25.30	0.97		0.34	1.23
3		1.52	0.86	3	10.50	0.72	11	12.40	0.74		0.27	0.90
4	*	0.83			1.32	0.63		0.39	0.65		1.04	0.98
5		0.44	0.61		0.26	0.66		0.42	0.73	11	11.35	0.90
6		0.86	0.88		0.37	0.69		0.69	0.66	1	28.50	0.74
7		0.35	0.85		0.25	0.94		0.16	1.25		0.43	0.65
8		0.68	0.70		0.63	0.87		0.40	0.77		0.15	1.03
9					0.44	0.74		0.36	0.76			
		Calculated net recovery										
	12	40.42	1.79	12	41.21	2.63	12	36.70	3.26	12	39.93	2.60

\* No stool sample.

subjects in experiment 2 excreted relatively little of net thiamin in the urine, from 1.8 mg. by H. N. to 3.3 mg. by J. H. On the other hand, they excreted large quantities in the feces, from 36.7 mg. by J. H. to 41.2 mg. by M. H. The approximately reciprocal relations between the urinary and fecal excretion should be noted. The total quantity recovered in the urine and feces, in the order of subjects given in Table II, were: 42.2, 43.8, 40.0, and 42.5 mg. The differences were within the limits of error of the collection of samples and the analytical method. The results thus obtained from the 4 subjects in experiment 2, with markedly differing rates of gastro-intestinal motility, suggest that the destruction of thiamin occurs largely in the tissues, a conclusion which is indicated also by the results of experiments 3 and 4.

*Equilibrium with thiamin orally administered three or four times per day*

*Experiment 3.* Four subjects (Table III) ate weighed diets containing the same ingredients, but differing in the proportions of some food items. Two subjects, T. F. and E. L., received 2500 calories per day, the total thiamin con-

TABLE III

*Experiment 3. Oral administration of increasing quantities of thiamin in three divided doses with meals and before meals*

The results represent the net daily average urinary and fecal excretions during the last 4 days of each period of 14 days. The initial average daily excretions, in the order of subjects given below, were: feces, 0.24, 0.34, 0.76, and 0.34; urine, 0.25, 0.29, 0.28, and 0.31 mg.

TOTAL SUPPLEMENT PER DAY	FECES		URINE			NOT RECOVERED IN FECES AND URINE
	Recovered	Absorbed or not recovered	Recovered	Percentage excreted		
Subject	T. F.	Thiamin taken at meals, diet of 2,500 cal. contained 1.18 mg. B <sub>1</sub>				
mg.	mg.	mg.	mg.	*	†	mg.
3.66	-0.01	3.66	1.19	33	33	2.48
7.32	0.29	7.03	2.70	37	38	4.33
10.83	2.98	7.85	3.91	36	50	3.94
19.38	7.04	12.34	5.44	28	44	6.90
40.62	30.34	10.28	6.86	17	67	3.42
Subject	M. H.	Thiamin taken at meals, diet of 3,000 cal. contained 1.31 mg. B <sub>1</sub>				
3.66	0.15	3.51	1.28	35	36	2.23
7.32	1.05	6.27	2.78	38	44	3.49
10.83	3.11	7.72	3.84	35	50	3.88
Subject	J. H.	Thiamin taken 1 hour before meals, diet of 3,000 cal. contained 1.31 mg. B <sub>1</sub>				
3.90	0.27	3.63	1.28	33	35	2.35
7.32	1.32	6.00	1.86	25	31	4.14
10.83	2.33	8.50	3.19	29	38	5.31
Subject	E. L.	Thiamin taken 1 hour before meals, diet of 2,500 cal. contained 1.18 mg. B <sub>1</sub>				
3.90	0.15	3.75	1.08	28	29	2.67
7.32	1.81	5.51	1.97	27	36	3.54
10.83	3.50	7.33	2.67	25	36	4.66

\* Based on ingested thiamin.

† Based on apparent absorption of thiamin (column 3).

tent being 1.18 mg. The other 2 subjects, M. H. and J. H., received 3000 cal. per day, the total thiamin content being 1.31 mg. The control period was 14 days, after which thiamin supplements in tablets were given 3 times per day either with the meal or 1 hour before the meal. The quantity of thiamin given per day was increased in steps during periods of 14 days each. One of the

subjects, T. F., continued the experiment until 13.54 mg. was taken at each meal, or a total of 40.62 mg. per day.

The experiment was designed to test the effect of taking the supplement with the meals and between meals. In the latter instance, the vitamin was perhaps less exposed to the action of HCl and bile, which are important constituents of digestive juices and which may conceivably alter the utilization. Accordingly, the effect of these conditions was determined on 2 subjects, J. H. and E. L., during several periods as shown in Table IV. Thereafter, these subjects received supplements of 7.32 and 10.83 mg. in 3 divided doses before meals as shown in Table III.

TABLE IV

*Experiment 3. Oral administration of 3.90 mg. thiamin supplement in 3 divided doses*

The results represent the net average daily urinary excretion of thiamin. The 6 experimental periods followed the control period during which J. H. and E. L. excreted an average of 0.28 and 0.31 mg., respectively, of thiamin per day; they were followed by the experimental periods of 14 days each shown in Table III.

PERIOD NO.	3.90 MG. THIAMIN PLUS DIET AND OTHER SUPPLEMENTS	DURATION OF EXPERIMENTAL PERIOD	SUBJECT J. H.	SUBJECT E. L.
Thiamin supplement taken at each of the 3 meals				
1	Diet only	days 14	mg. 1.43	% 37
Thiamin and other supplements taken 1 hour before each of the 3 meals				
2	Diet only	14	1.28	33
3	Diet + 60 cc. 0.1 N HCl	4	1.25	32
4	Diet + 300 mg. bile salts	2	1.21	31
5	Diet + HCl + bile salts	2	1.20	31
6	Diet only	6	1.28	33
			mg. 1.44	% 37
			mg. 1.03	26
			1.03	26
			1.12	29
			1.10	28
			1.13	29

The "utilization" of thiamin by each subject, as measured by the per cent of the supplement which was excreted (column 5), was apparently unchanged at the levels of 1.22 to 3.61 mg. extra thiamin per meal, or at a total of 3.66 to 10.83 mg. per day, in spite of the large excretion of fecal thiamin at the latter level. The per cent of the supplement thus excreted was characteristic and apparently quite constant for each subject: from about 26% in the case of E. L. to approximately 36% in the case of T. F.

At an intake of 1.22 mg. of supplement per meal, most of the thiamin was absorbed by subject T. F. However, appreciable quantities were excreted in the feces at this level by the other subjects. Considerably larger quantities were excreted in the stools at the level of 2.44 mg. per meal, or 7.32 mg. per day. It would seem, therefore, that the maximum of supplement which can

be absorbed completely is about 1 mg. at each meal, or a total of about 5 mg. per day when the thiamin content of the diet is considered.

The data in the third column of Table III represent the difference between the total quantity of supplement ingested and the average net total excretion in the feces per day. They probably represent the quantities which were absorbed. The quantities thus absorbed, or not recovered, increased rapidly at each level of intake and reached calculated values varying from 7.33 to 8.50 mg. per day at a total intake of 10.83 mg. per day.

*These observations on the apparent absorption, when compared with the relatively constant percentage recovery of thiamin in the urine up to total supplements of 10.83 mg., indicate the fallacy of determinations of "utilization" based solely upon urinary excretion<sup>16, 17</sup>.* Thus, the calculated data which are based upon the apparent absorption (Column 6, Table III) with few exceptions, show increasing percentages of excretion at increasing high levels of intake.

In the case of subject T. F., the quantity of fecal thiamin increased progressively with supplements of 6.46 and 13.54 mg. at each meal, or 19.38 and 40.62 mg. per day. At these levels, 36 and 75%, respectively, of the thiamin were recovered in the stools; however, the total quantity which was not recovered in the feces and which presumably was absorbed, was relatively constant. Thus, in spite of large quantities of thiamin which were always present in the intestinal tract, only 12.34 and 10.28 mg. were absorbed.

The "free" thiamin content of the stools of T. F. determined immediately on each of 2 days at the last 2 levels of intake was as follows: 88 and 73% at 19.38 mg. intake per day; 78 and 84% at 40.62 mg. intake per day.

The quantity not recovered either in the urine or feces is shown in the last column of Table III. It is the fraction which was either destroyed in the intestinal tract, stored in the tissues, or destroyed in the tissues—or the result of the three processes. Since the subjects had reached a state of equilibrium with the ingested vitamin before the period of collection of samples, it may be assumed that storage of thiamin did not play a significant part in the utilization as represented by this fraction. Therefore, the unrecovered quantity probably represents the fraction which was destroyed.

Of the 3.66 mg. administered daily to each subject in the first period, and which was almost completely absorbed, from 2.23 to 2.67 mg. were not recovered. The quantity not recovered was increased considerably, from 3.49 to 4.33 mg., at the level of 7.32 mg. per day; it was further increased slightly, from 3.88 to 5.31 mg., at the subsequent level of 10.83 mg. per day. At the higher levels of 19.38 and 40.62 mg., subject T. F. "utilized" 6.90 and 3.42 mg., respectively, in this manner. At the higher levels, the analytical errors are increased and the errors in collection of urine and stools are thus multiplied. Variations of at least  $\pm 2$  mg. may be expected when errors of  $\pm 10\%$  for fecal

collections and analyses, and  $\pm 5\%$  for urinary collections and analyses, are assumed. The variations in the results shown in the last column, Table III, fall within this range. On the whole, the results indicate a maximum utilization or non-recovery of thiamin at a daily level of intake at or about 7 mg. of supplement per day.

Subjects T. F. and M. H., who received 3.66 mg. thiamin in 3 divided doses with meals, excreted 33 and 35% as compared with 33 and 28% excreted by J. H. and E. L. who received 3.90 mg. in 3 divided doses 1 hour before meals (Table III). Thus, no differences in excretion were apparent under the 2 conditions of administration. However, J. H. and E. L. excreted 37 and 37% when the vitamin was given with food in a previous period (Table IV). Although the data are limited to only 2 subjects, they support the conclusions of Melnick, Field and Robinson<sup>8</sup> that greater utilization is achieved when the vitamin is given with food.

The excretion was not increased (Table IV) when HCl, bile salts, or HCl plus bile salts were given simultaneously with the vitamin 1 hour before meals. These substances were given in order to simulate some of the conditions during digestion and absorption.

*Experiment 4.* The object of this experiment was to determine the utilization of thiamin chloride and thiamin mononitrate\* at levels of 30 or 40 mg. of supplement per day. Since the administered quantities were large, a weighed diet was not as essential as in experiment 3. However, each subject adhered to his usual diet, with approximately the same servings of the chosen food items at each meal throughout. One tablet, containing an average of 10.1 mg. thiamin, was taken at each of the 3 meals during the first experimental period; during the second experimental period, a fourth tablet was taken with a sandwich and 1 glass of milk at 9:30 p.m. Thiamin mononitrate was taken in 3 divided doses of exactly 10.0 mg. each, calculated as thiamin chloride hydrochloride. The preliminary control period was 10 days, and each of the 3 experimental periods were 10, 10, and 13 days, respectively. Urine and feces were collected during the last 5 days of each period, during which the subjects had from 6 to 8 bowel movements. The calculated net daily averages are given in Table V.

The results with thiamin chloride confirm those of the previous experiment with subject T. F. at the levels of 19 and 40 mg. supplements per day (Table III). The quantities recovered in the stools (Table V) varied according to the intake: from 16.4 to 22.5, or an average of 19.4 mg. with 30.3 mg. of supplement; from 28.1 to 29.9, or an average of 29.0 mg. with 40.4 mg. supplement. However, in spite of the large average differences in the fecal thiamin content during the 2 experimental periods, the quantities not recovered in the stools,

\* Thiamin mononitrate was supplied by Merck and Company, Rahway, New Jersey.

and thus presumably absorbed (column 3), were in approximately the same range: from 7.8 to 13.9, or an average of 10.9 mg. with 30.3 mg. daily supplement; from 10.5 to 12.3, or an average of 11.4 mg. with 40.4 mg. daily supplement.

The results of the third series in experiment 4 suggest that thiamin mononitrate is absorbed, excreted and destroyed in the body at rates similar to that of thiamin chloride hydrochloride.

TABLE V

*Experiment 4. Oral administration of thiamin chloride and thiamin mononitrate in divided doses with meals*

The results represent the calculated net daily excretion, expressed as thiamin chloride hydrochloride, during the last 5 days of each experimental period. Each subject adhered to his own chosen "normal" diet. During the control period of 10 days, subjects N. F., M. and J. B. excreted the following average quantities of thiamin: feces, 0.51, 0.52, and 0.58; urine, 0.47, 0.44, and 0.26 mg. per day. Subject G. G. excreted 0.32 and 1.27 mg. per day, respectively, of urinary and fecal thiamin during a similar 10-day control period.

SUBJECTS	FECES		URINE RECOVERED	NOT RECOVERED IN FECES AND URINE
	Recovered	Absorbed or not recovered		
<b>30.3 mg. thiamin chloride in 3 divided doses; 7 a.m. October 17 to 7 a.m. October 27</b>				
J. B.....	mg. 22.5	mg. 7.8	mg. 4.0	mg. 3.8
M.....	19.4	10.9	5.5	5.5
N. F.....	16.4	13.9	6.4	7.5
<b>40.4 mg. thiamin chloride in 4 divided doses; 7 a.m. October 27 to 7 a.m. November 6</b>				
J. B.....	29.0	11.4	8.0	3.4
M.....	29.9	10.5	8.6	1.9
N. F.....	28.1	12.3	9.2	3.1
<b>30.0 mg. thiamin mononitrate* in 3 divided doses; 7 a.m. December 1 to 7 a.m. December 14</b>				
J. B.....	17.1	12.9	7.4	5.5
M.....	17.6	12.4	9.2	3.2
G. G.....	16.4	13.6	6.2	7.4

\* Calculated as thiamin chloride hydrochloride.

In summary, the combined data obtained with thiamin chloride in experiments 3 and 4 give the following calculated average daily values. Of 8 observations on the quantity "absorbed", or not recovered in the feces, at 19 to 40 mg. daily intake, 6 fell within the range of 10.3 to 12.3 mg., with an arithmetic mean of 11.2 mg. and a standard deviation of 1.7 mg. Sixteen observations on the over-all "utilization", or the quantity not recovered in stools and urine, with daily supplements of 7 to 40 mg., fell within a range of 1.9 to 7.5 mg., whose arithmetic mean was 4.31 mg. and whose standard deviation was

1.8 mg. Ten of the 16 observations fell within a range of 3.1 to 4.3 mg., with an arithmetic mean of 3.70 mg. and a standard deviation of 0.36 mg.

*Experiment 5.* This experiment (Table VI) is presented because of the marked departure of the results from those of the previous experiments. The

TABLE VI

*Experiment 5. Oral administration of thiamin chloride hydrochloride*

Mrs. J. B. ate the same diet during a control period of 17 days and two experimental periods totaling 38 days. The average daily urinary excretion of thiamin during the control period was: from the fifth to tenth days, 0.173; from the eleventh to seventeenth days, 0.170 mg. She had only 5 bowel movements in the last 14 days of the control period. The average daily fecal thiamin excretion was 0.48 mg.

DAY OF EXPERIMENTAL PERIOD	URINE, TOTAL THIAMIN PER DAY	FECES		CALCULATIONS
		Weight of sample	Total thiamin of sample	
50.0 mg. thiamin in single dose, October 24				
1	1.440			mg. net thiamin 10-day period
2	0.341			Total ingested..... 50.0
3	0.271	178	4.30	Urine..... 1.71
4	0.218			Feces..... 23.19
5	0.216			Total recovered..... 24.90
6	0.224	228	19.90	Total "destroyed"..... 25.10
7	0.220			
8	0.165	183	2.45	
9	0.154			
10	0.176	148	1.34	
40.4 mg. thiamin each day in 4 divided doses, Nov. 8 to 30, inclusive				
3		226	8.4	Last 10 days†
6		171	43.1	Total ingested..... 404.0
13	9.70*	91	36.0	Urine..... 96.3
14		193	68.6	Feces..... 218.2
16	10.00*	219	74.4	Total recovered..... 314.5
23	9.69*	216	80.0	Total "destroyed"..... 89.5

\* Average daily excretion obtained by analyses of composite samples from experimental days inclusive as follows: 11 to 15, 16 to 20, and 21 to 23.

† The third sample of this period, containing 36 mg., was obtained at 8:15 a.m. November 20; the last at 10:00 a.m. November 30. Therefore, the time during which the last 3 samples were collected was approximately 10 days.

subject, Mrs. J. B., had been constipated over a period of several years. In the 55 days of the experiment, only 17 stool samples were obtained, at an average interval of 3.24 days. Only 3 stools—2 in the control period—were eliminated at 1-day intervals; 1 at a 5-day interval, from the tenth to the fifteenth

day of the first experimental period; 2 at 7-day intervals in the second experimental period. The stools were large, well-formed, but hard.

The experiment was divided into 3 periods; a control period of 17 days; a period of 15 days following a single ingestion of 50.0 mg. thiamin as in experiments 1 and 2; and a final period of 23 days during which 40.4 mg. thiamin were taken in 4 divided doses each day as in experiments 3 and 4. Each experimental period was begun immediately after the last stool sample of the preceding period had been collected.

Results similar to those of experiments 1 and 2 were obtained with respect to urinary excretion after ingestion of a single dose of 50.0 mg. The excretion was highest on the first day. It diminished rapidly, and on the eighth day came within the range of the control period. The average excretion from the eleventh to the fifteenth days\* inclusive was 0.171 mg. as compared with 0.1715 mg. in the control period. Again, as in experiments 1 and 2, the urinary excretion approached the control level before all of the fecal thiamin was excreted. The net total quantity recovered in 10 days was only 24.90 mg. Therefore, the quantity destroyed was 25.10 mg.

During the second experimental period, the urinary excretion at daily levels of 40.4 mg. supplement was slightly higher than in experiments 3 and 4, although the feces contained from 2 to 3 times as much thiamin. The net daily excretion of 9.63 mg. during a 10-day period suggests that the intestinal absorption was about the same as in the subjects (experiment 4) with normal intestinal motility. This again demonstrated the limited intestinal absorption.

However, the calculated daily quantities excreted in the feces was much less than in the previous experiments. Because of the small number of samples, the over-all utilization could not be determined with any degree of accuracy. The difference between the intake and fecal excretion was 404.0 - 218.2, or 185.8 mg., in the last 10 days. Thus an average of 18.58 mg. per day was presumably absorbed, which is not in accord with the magnitude of the urinary excretion. The average calculated quantity destroyed per day was 8.95 mg.

#### DISCUSSION

Our data from 14 human subjects demonstrate the very limited absorption of thiamin from the intestinal tract. Supplements of 1.0 mg. taken with 3 meals each day are presumably absorbed completely since the thiamin content of the feces is not increased. If the vitamin content of the diet is considered, perhaps the maximum of *complete absorption*, and therefore, the maximum economical level of intake is about 5 mg. per day. As the daily intake is increased, the rate of absorption rises somewhat, and progressively larger quantities are excreted in the feces. The maximum absorption of 8 to 14 mg. is attained with

\* In order to conserve space, the data on the last 5 days of the period are not given. A stool sample collected on the fifteenth day contained 1.28 mg. thiamin.

daily supplements of 20 to 40 mg.—perhaps with 15 mg.—given in 3 or 4 divided doses with food.

The results have clinical interest because they indicate that oral doses of more than 5 mg. are largely wasted. When the use of large doses, or a high concentration in the blood, is desired in treatment, the vitamin should be administered parenterally. Furthermore, in contrast to other vitamins, the continued administration of thiamin occasionally leads to development of an allergic response.

However, the data have another interest because they indicate the probable magnitude of maximal absorption of substances whose entrance into the blood stream is accomplished by apparently incidental means rather than by simple diffusion or by specific mechanisms. At least several hundred mg. of the following vitamins differing greatly in structure are readily absorbed: riboflavin, niacin, pyridoxine, pantothenic acid, and vitamin C. These substances, like thiamin, are normal and necessary constituents of all tissues. On the other hand, a large number of synthetic drugs, sulfathiazole among them, are rapidly absorbed when given in 65 mg. or larger doses. The small rate of absorption of thiamin is further apparent when compared with that of dextrose. Both are very soluble, rapidly diffusible through organic membranes and readily phosphorylated; yet from 50,000 to perhaps 100,000 times more of dextrose (600 gm.) may be absorbed completely in 24 hours by adult human beings. Such considerations lead us to assume a very efficient barrier mechanism for thiamin in the intestinal tract, which probably was evolved to prevent the entry of a category of substances harmful, or as such not immediately useful, to the organism. A special mechanism for thiamin is not needed because the small quantity that can be absorbed is greater than the optimal daily requirement.

It is inconceivable that entrance of any readily diffusible substance or ion can be entirely prevented across cell boundaries however well the cell may be provided with mechanisms which protect the integrity of the organism. This is true particularly when the large number of cellular units which line the 10 sq. m. or so<sup>25</sup> of the intestinal tract are considered. The observed range of thiamin absorption may well be representative of similar, apparently non-absorbable or non-transferable, substances of relatively small molecular weight.\*

The maximum quantity of thiamin "utilized" or destroyed in the intestinal tract and tissues is about 4 mg. per day in subjects who have at least 1 normal

\* Streptomycin, which generally is considered "non-absorbable", perhaps belongs in this category. Most investigators have noted none or only traces in plasma and urine after oral administration. Adcock and Hettig<sup>26</sup> recovered from 0.2 to 0.5% in urine when 4,000,000 units (equivalent to 4000 mg. streptomycin A base) were given in 8 divided doses daily for 6 days. Assuming that 75% of the absorbed base was excreted, from 11 to 27 mg. were thus absorbed.

The absorption of iron, which normally is quite limited and, like thiamin, confined largely to the upper intestinal tract, is markedly increased in hypochromic anemias. Is the absorption of thiamin similarly greater in the thiamin-depleted than in the normal subject? This question will be discussed in a subsequent communication.

bowel movement per day. The destruction probably occurs largely in the tissues, first, because approximately equal quantities are not recovered when a single large dose of 50 mg. is given (experiment 2). Second, the destruction is about the same when daily supplements of 7 to 40 mg. are given in 3 or 4 divided doses over an extended period of time (experiments 3 and 4). In the latter instance, the average daily fecal excretion may vary from 0.3 to 1.8 mg. with 7 mg. of supplement to 28 to 30 mg. with 40 mg. of supplement. The results thus suggest an approximately constant rate of destruction of thiamin in the tissues when quantities of about 6 to 14 mg. per day are absorbed. Alexander, Landwehr and Mitchell<sup>16</sup> reached the same conclusion with respect to the formation and excretion of "pyrimidine activating yeast fermentation (PAYF);" at doses of more than 10 mg., *injected intramuscularly*, "the maximal amount of thiamine which the body can convert to pyrimidine has been reached and the rest of the thiamine is excreted as such." In substantial agreement with our data, the average maximal PAYF excretion was equivalent to 5 mg. thiamin (see reference 15, cf. Fig. 5, p. 301), which lends further support to our view that destruction of orally administered thiamin occurs largely in the tissues. This apparent constant maximal destruction, which is attained at levels of intake well above "saturation", is due perhaps to the rapid rate of renal excretion which tends to maintain a relatively low and constant level of thiamin in the plasma. This phase of the subject will be presented in a subsequent paper.

Undoubtedly some of the vitamin is destroyed in the intestinal tract, which was indicated in experiments with 2 subjects who were constipated and had scanty stools (experiment 1) or infrequent bowel movements (experiment 5). The results when compared with those of the other experiments suggest that the colon is the site of the greatest intestinal destruction.

#### SUMMARY AND CONCLUSIONS

Thiamin was administered orally as follows after initial control periods of 14 to 20 days: (1) in a single dose of 50 mg.; (2) in daily doses varying from 3.66 to 40 mg., given in 3 or 4 divided doses with food or 1 hour before meals, during periods of 10 to 14 days. The thiamin content of stools and urine was determined by the thiochrome procedure.

The intestinal absorption of thiamin chloride hydrochloride by normal human subjects is extremely limited. The maximum which could be taken orally without an increase of fecal thiamin was about 5 mg. per day, or slightly less than 2 mg. including thiamin in food, at each meal or single ingestion. At a total intake of 5.1 to 5.2 mg. per day, the urinary excretion was greater when the vitamin supplement was given with meals than when given 1 hour before meals; under the latter conditions, the excretion was not increased by simultaneous administration of HCl, bile salts, or HCl plus bile salts. At levels of

19 to 40 mg. per day, given in 3 or 4 divided doses, 8 to 14 mg. were absorbed or not recovered in the feces. Of 8 observations on the absorption by 4 subjects at these levels of supplements, 6 fell within the range of 10.3 to 12.3 mg.; the mean of all determinations was 11.2 and the standard deviation, 1.7 mg. The "free" thiamin content of the feces of one subject at levels of 19 and 40 mg. supplement per day varied from 73 to 88%.

Thiamin mononitrate was absorbed, excreted and destroyed at rates similar to that of thiamin chloride hydrochloride.

The maximum quantity destroyed in the intestinal tract and tissues was about 4 mg. per day in subjects with normal intestinal motility receiving from 7 to 40 mg. supplement per day. The principal site of destruction is in the body tissues; variable quantities may be destroyed in the colon.

Thiamin apparently belongs to that group of substances which are relatively poorly absorbed in the gastrointestinal tract, the maximum economical level of intake being about 5 mg. per day.

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# A STUDY ON THE OCCURRENCE OF PNEUMOPERITONEUM AFTER GASTROSCOPY AND THE OBSERVANCE OF INTERSTITIAL EMPHYSEMA OF THE STOMACH\*

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Thirteen cases of pneumoperitoneum have been reported after gastroscopy<sup>1, 2, 3, 4, 5, 6, 7, 8, 9</sup>. Because of the very minimal reactions to the accidents, it was felt it could possibly be a more common incident than expected from the small number of case reports.

Therefore, twenty-four hours after 119 consecutive gastroscopic examinations, using a flexible gastroscope with a rubber finger-tip, upright x-ray films of the abdomen were made.

The typical pneumoperitoneum was not found. In two instances, however, there were abnormal x-ray findings of a thin line of decreased density, presumably air, in the left upper quadrant of the abdomen closely approximating but separate from the air bubble in the stomach.

The first case was a fifty-three year old white laborer admitted to the hospital 14 July 1947 complaining of an acute exacerbation of chronic epigastric distress dating back at least eight years. In 1942 a perforated peptic ulcer had been closed by operation. Gastro-intestinal x-ray examination on this admission showed a deformed duodenal bulb with a crater and a suggestion of a pseudo-polyp in the antral region of the stomach. Evening gastric aspirations persistently yielded 320 to 450 cc. An uneventful gastroscopy was performed on 1 August 1947. The mucosa appeared normal but the superior half of the pylorus and the pre-pyloric area on the lesser curvature were not visualized due to a distorted pre-pyloric canal. Upright x-ray film of the abdomen twenty-four hours after gastroscopy demonstrated an area of decreased density in the left upper quadrant as shown in figure 1, which was originally interpreted as pneumoperitoneum, but Dr. Leo G. Rigler suggested it was interstitial emphysema of the stomach wall. The patient was up and about the ward, going to the dining room, and had no complaints whatever. Unfortunately white blood cell counts and erythrocyte sedimentation rates were not obtained. There was no change in temperature. Pre-gastroscopy pulse rate averaged about 80 beats per minute and for three days after gastroscopy averaged 95 beats per minute. Subtotal gastrectomy on 25 August 1947 disclosed a gastric ulcer four mm. in diameter on the lesser curvature close to the pylorus.

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FIG. 1 (Case 1). X-ray film of the left upper quadrant of the abdomen in the upright position taken twenty-four hours after gastroscopy showing the thin line of decreased density superior, medial and separate from the air bubble of the stomach.



FIG. 2 (Case 2). X-ray film of the left upper quadrant of the abdomen in the upright position twenty-four hours after gastroscopy showing the thin line of decreased density superior, medial and separate from the air bubble of the stomach.

The second case was a nineteen year old white male student and amateur boxer with no definite previous gastro-intestinal symptoms who was admitted to the hospital on 1 September 1947 with x-ray evidence of acute dilatation of the stomach after severe cramping abdominal pains with vomiting for twenty-four hours. Continuous gastric suction relieved all symptoms. Urinalysis, Kahn, chest plate, gastro-intestinal x-ray series, gastric analysis, barium enema, cholecystogram, stool examinations for ova, parasites, and occult blood, proc-



FIG. 3. (Case 2). Same patient same exposure as Fig. 2 taken forty-eight hours after gastroscopy. A lateral decubitus film taken at the same time showed the area of decreased density to be separate from the air bubble of the stomach. At seventy-two hours the air had disappeared.

toscopy, blood cephalin-cholesterol flocculation and serum bilirubin were normal. On 10, 11, and 12 September the evening gastric aspirations were 30, 70, and 80 cc. respectively. Gastroscopic examination on 13 September 1947 was uneventful and the mucosa and the pyloric action were normal. On 14 September 1947 routine upright post-gastroscopy roentgenogram of the abdomen showed an area of decreased density in the left upper quadrant as described in detail in figure 2. The patient was up about the ward and going to the dining room. He had no complaints except a slight sore throat. Leukocyte count and differential, erythrocyte sedimentation rate, and temperature

were normal. The pulse rate pre-gastroscopy averaged about 85 beats per minute and for the first three days post-gastroscopy averaged 100 beats per minute. He was discharged 19 September 1947 as an acute dilatation of the stomach cause undetermined. In December 1947 he had no gastro-intestinal complaints and gastroscopy, gastro-intestinal x-ray series, and post-gastroscopy upright x-ray film of the abdomen were negative. There was no tachycardia after gastroscopy.

#### DISCUSSION

No cases of pneumoperitoneum were found in 119 consecutive x-ray examinations of the abdomen in the upright position twenty-four hours after gastroscopy. In two instances there were x-ray findings suggesting interstitial emphysema of the stomach wall.

This x-ray interpretation is in accord with the findings of Chamberlin<sup>8</sup> at operation in a case of pneumoperitoneum after gastroscopy. He described emphysematous blebs along the lesser curvature extending up into the fundus.

Both cases were asymptomatic and only a slight tachycardia was noted. Six of sixty patients surveyed had a tachycardia of 90 to 100 beats per minute during the first three post-gastroscopic days. In the second patient daily leukocyte counts and erythrocyte sedimentation rates were normal. Obviously without the x-ray there would have been no knowledge of the occurrence.

Previous reports<sup>6, 7, 8</sup> comment on the lack of evidence to suggest perforation of the stomach wall by the gastroscope. We feel that such a perforation is probably not necessary but that interstitial emphysema is one of the steps in the progression to gross leakage into the peritoneal cavity. Dilated lymphatic vessels and peri-neural lymphatic vessels as observed by Chamberlin<sup>8</sup> are possibly the starting point.

#### CONCLUSIONS

1. 119 consecutive cases were studied for pneumoperitoneum twenty-four hours after gastroscopy by upright x-ray studies of the abdomen. This was undertaken to determine the incidence of this apparently fairly innocuous accident.

2. No cases of pneumoperitoneum were discovered but in two cases a thin line of decreased density in the left upper quadrant in close approximation but separate from the air bubble of the stomach was observed. This was interpreted as interstitial emphysema of the stomach wall and was asymptomatic.

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## CASE REPORTS

### A CASE OF INTESTINAL LIPODYSTROPHY (WHIPPLE'S DISEASE) SIMULATING BOECK'S SARCOID\*

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#### INTRODUCTION

Since Whipple<sup>20</sup> first described a disease in 1907 for which he used the term "intestinal lipodystrophy" there have been about 22 additional cases reported<sup>2-5, 7-9, 11-19</sup> with many names and theories as to the pathogenesis of the condition. Such terms as lipophagic granulomatosis, malabsorption of fat and mesenteric chyladenectasis have been suggested. Recently excellent reviews of the condition have been presented<sup>7, 15, 17</sup>.

Of the 22 reported cases, four patients were still alive after their disease had been diagnosed by biopsy of the mesentery<sup>14, 15</sup>. We believe the present case is the nineteenth to be studied at autopsy and reported.

The majority of reported cases have been in men whose main complaints were diarrhea and progressive loss of weight associated with symptoms referable to deficiencies in vitamins, proteins and other essential food factors. Symptoms varied from a few months to 15 years in duration.

The physical conditions are usually described as marked emaciation and nutritional deficiencies. Many cases have shown slight enlargement of the axillary and inguinal lymph nodes. The abdomen is sometimes negative, but it may be described as feeling heavy, thick-walled or doughy and occasionally the mesenteric nodes are palpable as abdominal masses.

There is usually an associated iron deficiency type of anemia. Leucocytosis is unusual and there is often a normal differential count or slight lymphocytosis. The stools may or may not show increase in the fat content but otherwise they may be normal. Serum protein, calcium and vitamin levels may be low as in any other chronic diarrheal disease.

The following case has certain findings which make it unique.

#### REPORT OF CASE

A 50-year-old trainman was admitted January 28, 1947 complaining of weakness, excess fatigue and loss of weight. He had been ill for two years with recurrent episodes of diarrhea varying with obstipation. At times the diarrhea

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was severe causing marked anorexia. At other times he would be constipated for days during which he would notice swelling of his abdomen and crampy pain. His illness was characterized by increasing anorexia and loss of weight. His weight dropped from 185 pounds to 90 pounds in two years. One month before admission he was operated on at another hospital presumably with a preoperative diagnosis of intestinal obstruction. He was told that he had "many small tumor glands" in his abdomen. The pathologist reported Boeck's sarcoid, atypical. He recovered uneventfully, but symptoms continued.

At the time of admission his temperature was normal. He had the appearance of being a well developed, but extremely emaciated, chronically ill man. The skin was dry and scaly. The eyes were normal except for increased vascularity of the conjunctivae and the patient complained often of burning of the eyes. The heart and lungs revealed no abnormalities on clinical examination. The blood pressure was 90/60. The abdomen was always slightly distended, peristaltic waves could be seen through the thin abdominal wall. There was a well healed right rectus scar. On palpation the abdomen felt thick and doughy. No masses were felt.

The red blood count varied between 3 and 3.5 million cells with 8.0 to 9.0 grams of hemoglobin; white blood counts about 7,500. The differential count was: neutrophils 57 per cent; lymphocytes 40 per cent; and 3 monocytes. Stained smears were consistent with a diagnosis of a hypochromic microcytic anemia. Prothrombin time was 87 per cent of normal. Bleeding and coagulation times were normal. The non-protein nitrogen was 39 mg. per 100 cc. On admission the total serum proteins was 5.7 Gm. per 100 cc. with 3.2 Gm. of albumin and 2.5 Gm. of globulin; serum calcium and phosphorus levels were normal.

X-ray examination of the chest, esophagus and colon was considered normal. A small bowel series revealed areas of puddling of the barium and loss of the normal pattern.

The patient was placed on a high caloric diet with parenteral vitamins and protein hydrolysates, but this therapy was defeated by the marked anorexia of the patient. In spite of parenteral and tube feedings the symptoms continued unabated. Diarrhea was present as 5-10 semi-solid movements a day. Studies of stool revealed no ova, parasites or pathogenic bacteria. Stools were not voluminous and did not have the characteristics of those seen in sprue; fat content was normal. Two months after admission the patient developed rather marked pitting edema of the legs and sacrum and at the same time his total serum proteins fell to 4.6 Gm. per 100 cc. with 2.5 Gm. of albumin and 2.1 Gm. of globulin. He was treated with human albumin with rather rapid disappearance of edema, but symptoms progressed. In spite of parenteral and

oral calcium the serum level fell to 9.0 mg. per 100 cc. and at times the patient exhibited the muscular hyper-irritability of calcium deficiency.

The patient was treated symptomatically and given folic acid as certain types of diarrhea and nutritional diseases have been greatly aided by this drug. After nearly seven months of unsuccessful treatment the patient died suddenly.

#### AUTOPSY FINDINGS

The body was that of a poorly developed, markedly emaciated white man appearing to be about 55 years of age. The skin was sallow and no icterus was seen. Both pleural cavities were obliterated by dense, gray white fibrous adhesions. The peritoneal cavity and pericardial sac were not remarkable. The heart showed serous atrophy of the subepicardial fat and brown atrophy of the myocardium. The lungs were negative. The liver weighed 800 grams. The gall bladder and extra hepatic bile ducts revealed no gross abnormalities. The spleen weighed 40 grams and was atrophic. The pancreas weighed 60 grams. The pancreatic ducts appeared normal. The esophagus was negative. The stomach was dilated and contained four liters of a mucoid fluid. The duodenum was dilated and the mucosa was negative. The small and large intestines were slightly dilated and contained a moderate amount of liquid and fecal material which was yellow white in color and putty like in consistency. The wall of the small intestine was of normal thickness. The mucosa of the jejunum and ileum was normal in appearance except for flecks of minute yellow white material. The Peyer's patches were not discernible.

The mesentery was thickened, gray white and had the consistency of rubber. The mesenteric lymph nodes were enlarged up to 2 cm. in diameter, firm, discrete and gray white. The cut surfaces of the lymph nodes were pale yellow gray and presented a spongy appearance.

Examination of the remainder of the organs including the brain and pituitary gland showed no gross lesions. The thoracic duct was not dissected out.

#### MICROSCOPIC EXAMINATION

The important lesions were found in the intestinal tract and mesenteric lymph nodes. The lesions in the jejunum and ileum were similar (fig. 1).

The villi were decreased in size and were atrophied. Throughout the mucosa were dense accumulations of large mononuclear cells having an abundant cytoplasm with vacuolated or foamy cytoplasm (fig. 2). There were large dilated endothelial lined spaces throughout the mucosa. Similar changes were seen in the submucosa but to a lesser degree. The muscularis was normal. The serosa showed a nonspecific inflammatory reaction consisting of a few lym-

phocytes, plasma cells and fibroblasts. The large intestine was negative. Viewed under low power magnification, the mesenteric lymph nodes presented a "swiss cheese" appearance. This was seen to be due to numerous dilated endothelial lined spaces (fig. 3).

Staining with Sudan III showed that these lymphatic sinuses contained large amounts of red staining material. Surrounding these spaces were large multi-nucleated foreign body giant cells. Focal areas of accumulations of vacuolated



FIG. 1. HEMATOXYLIN AND EOSIN STAIN OF JEJUNAL MUCOSA SHOWING DILATED LYMPHATIC SPACES AND ACCUMULATIONS OF FOAMY MONONUCLEAR CELLS.  $\times 200$

macrophages were seen. In addition there was a varying admixture of small lymphocytes, plasma cells, polymorphonuclear leucocytes and fibroblasts. In one section pseudotubercles were found composed of fat-laden histiocytes surrounded by collagenous connective tissue and infiltrated with plasma cells, lymphocytes and rare polymorphonuclear leucocytes. The mesentery showed mostly fibrosis with collections of the mononuclear cells most of which were filled with a foamy or vacuolated cytoplasm.

*Pathological diagnosis:* Intestinal lipodystrophy (Whipple's disease); brown atrophy of the myocardium and liver; acute dilatation of the stomach; serous atrophy of the subepicardial fat; bilateral chronic fibrous pleuritis.

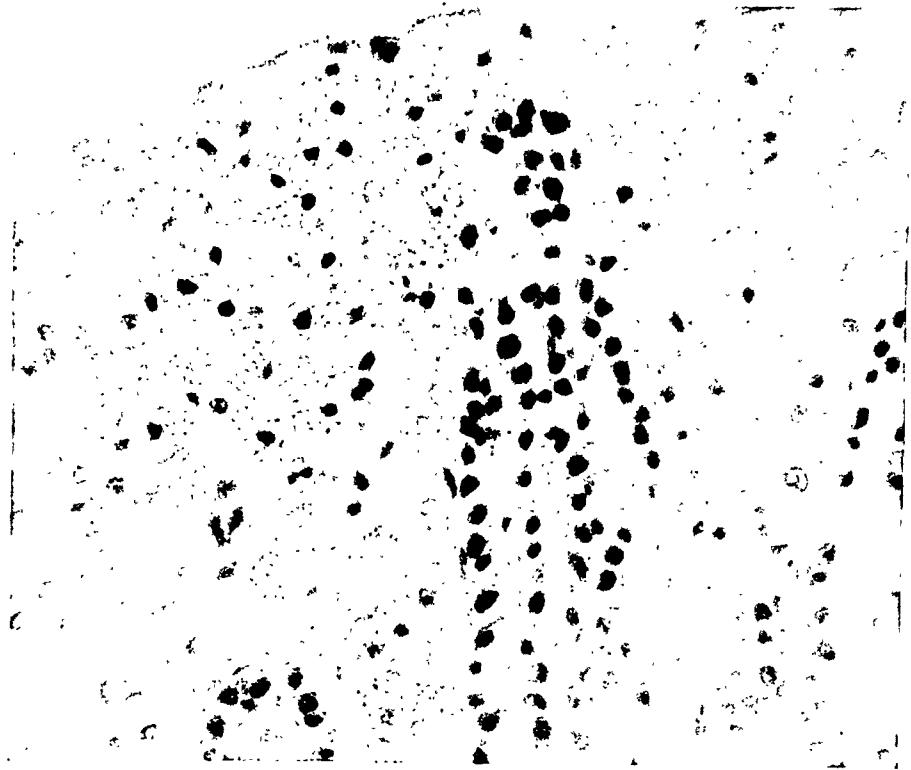


FIG. 2. HIGH POWER VIEW OF FIG. 1.  $\times 450$

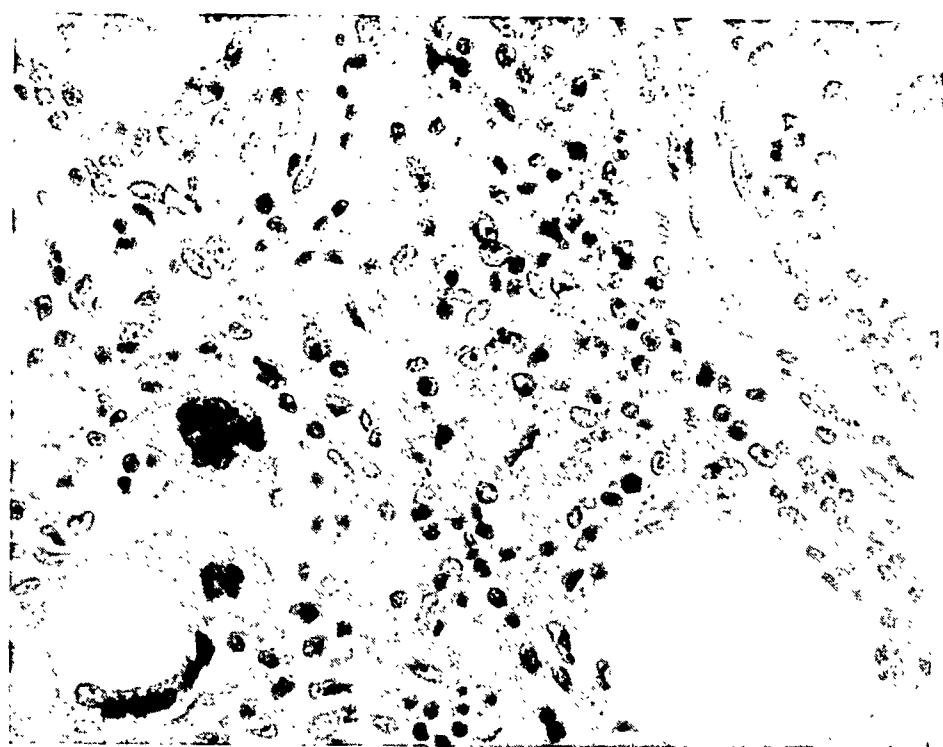


FIG. 3. HEMATOXYLIN AND EOSIN STAIN OF MESENTERIC LYMPH NODE SHOWING DILATED  
ENDOTHELIAL LINED SPACES, FOREIGN BODY GIANT CELLS AND INFLAMMATORY CELLS.  
 $\times 550$

## COMMENT

The genesis of this condition is unknown at the present time, but the following theories have been advanced:

1. Local necrosis of the fat tissue with liberation of lipolytic ferment from the damaged cells which act as foreign bodies producing a lipogranuloma.<sup>18</sup>
2. Dilatation of the lymphatics either obstructive or congenital.<sup>12</sup>
3. Experimentally Hass<sup>19</sup> produced lesions in animal tissues containing multi-

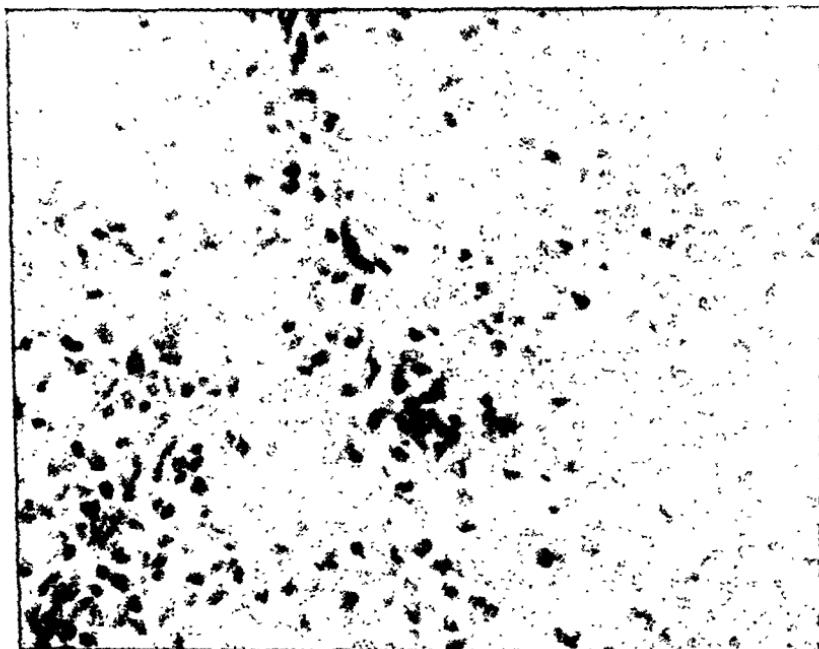


FIG. 4. HEMATOXYLIN AND EOSIN STAIN OF BIOPSED MESENTERIC LYMPH NODE SIMULATING BOECK'S SARCOID.  $\times 400$

nucleated giant cells and macrophages with foamy cytoplasm by injecting saturated fatty acids having a melting point above the body temperature.

4. Increased excretion of fat into intestines followed by increased re-absorption.<sup>16</sup>

This case does not enable one to subscribe to any one of the above theories, but the lesions of the lymph nodes and mesentery showed chronic inflammation, fibrosis and lymphatic dilatation which seemed further advanced and older than the process in the mucosa of the jejunum. This would suggest that the earliest changes occur in the lymph nodes of the mesentery rather than in the mucosa of the small intestine. Although the thoracic duct was not explored in the present case, there are cases<sup>6</sup> in which anatomic obstruction of the duct have

been demonstrated and these cases have presented the clinical manifestations of steatorrhea without evidence of deposition of fat in the lymph nodes.

Review of the sections obtained at operation in another hospital which were diagnosed as Boeck's sarcoid, showed the presence of miliary granulomas consisting of histiocytes laden with fat and infiltrations of plasma cells, lymphocytes, and polymorphonuclear leucocytes (fig. 4). Comparison of this slide with those of the autopsy material led us to believe that the biopsy material represented an earlier stage of intestinal lipodystrophy. It is of interest that Boeck<sup>4</sup> states that in one of his cases biopsy of an inguinal gland revealed a picture somewhat resembling tuberculosis, but there was no definite agreement. In his case, biopsy examination of one of the mesenteric lymph glands showed the picture of Whipple's disease.

Many cases of intestinal lipodystrophy have terminated with "sudden death" without any anatomic findings other than the described disease. The present case also terminated suddenly and death may be ascribed to acute dilatation of the stomach.

#### SUMMARY

A case is presented of moderately advanced intestinal lipodystrophy (Whipple's disease) which was mistaken for Boeck's sarcoid as a result of biopsy early in the disease. A brief summary of the theories in the literature are presented.

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## GASTROSCOPY FOLLOWED BY PNEUMOPERITONEUM WITH NO DISCERNIBLE LESION AT LAPAROTOMY THREE HOURS LATER

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### INTRODUCTION

Apparent rupture of the stomach during gastroscopy, followed by pneumoperitoneum, but without demonstrable lesion at laparotomy, has been reported in two instances. Schindler<sup>1</sup> described a case in 1945 in which air passed through the gastric wall in the course of a gastroscopy. During the examination dark red folds were seen for a few seconds. The stomach then collapsed, suggesting the entrance of air into the peritoneal cavity. Three hours later laparotomy was performed and escaping air produced a whistling sound when the peritoneum was opened. The stomach, inflated with oxygen and metylene blue under pressure, disclosed no lesion.

The second case reported by Berk in 1946<sup>2</sup> was one in which no rupture was reported to have been seen prior to the withdrawal of the gastroscope. Here again there was failure to inflate the stomach. Roentgenograms revealed air in the peritoneal cavity. The patient was in no distress until twelve hours later, when pain prompted operation. Escape of whistling gas and again an intact stomach were encountered. Each of these patients convalesced uneventfully.

To our knowledge the following is the third report of this condition in the literature and suggests a number of possibilities for discussion in the consideration of this peculiar phenomenon.

### CASE REPORT

The patient, F. A., No. 526,960, was a 65-year old white male who complained of pain in the epigastrium of many years' duration, recurrent hematemesis and tarry stools. In 1944 a tentative diagnosis of bleeding peptic ulcer was made during hospital study. At that time roentgen studies revealed no upper gastrointestinal lesion. Re-admission in April 1947 disclosed no suggestive organic pathologic changes in the stomach or duodenum.

Gastroscopy was performed July 1, 1947, after emptying the stomach with the Ewald tube. Minimal resistance was encountered at a point just beyond the cardia and, following a pause, the instrument was passed farther under direct vision. Normal orange-red mucosa was seen and, upon inflation, a dark slit-like opening, resembling a stoma, became clearly visible. Beyond this opening nothing was seen. With each unsuccessful attempt at inflation the two lips of the opening widened, exposing a

dark void beyond, following which the opening became slit-like again. The edges, resembling in a striking manner the lips of the mouth, were smooth and non-indurated. We were unable to visualize any other portion of the stomach. The aperture seemed to be in Depth III of the body on the lesser curvature.

A perforation was suspected at this juncture. The instrument was removed. The patient was pale but complained of little distress. Percussion note over the liver area was tympanic. Immediate fluoroscopy revealed air under the right diaphragm.

*Operation.* Suction was instituted preoperatively and laparotomy was performed by Dr. M. R. Gaspar. When the peritoneum was entered several hundred cc. of air escaped. The gastro-intestinal tract was thoroughly searched from the abdominal portion of the esophagus to the third portion of the duodenum, and no perforation could be found. The gastrocolic omentum was opened to facilitate the examination, and the stomach was greatly distended with air through an indwelling Levin tube and no air was found to escape. The abdomen was then closed. The patient had an uneventful postoperative course and progressed to complete recovery.

#### DISCUSSION

Leon Schiff is quoted by Schindler<sup>1</sup> as having encountered a case of pneumoperitoneum following the use of the flexible gastroscope without the occurrence of sudden deflation of the stomach. This apparently excludes his case from his group. It is interesting to note that, in the two cases quoted, the actual stomach rupture was not visualized. In the present case we were able to see the rent in the stomach very clearly and adequately, a fact which tends to establish the sequence of events more conclusively.

The explanation for the mechanism is obviously open to conjecture. The egress of air through a stomach wall which appears grossly intact at operation may be ascribed to a minute perforation in the serosa sufficient to allow air-passage followed by automatic self-sealing as the pressure drops. The fact that in our case we were unable to observe small bowel or peritoneal cavity lends weight to this conception. A large mucosal tear, with progressively lesser involvement of the other coats, has been suggested to explain our findings and may well be the explanation for the other cases.

In all three cases the patient recovered without need for surgical therapy. In the light of this fact, conservative expectant treatment, as opposed to surgical intervention, has been proposed. The fact that the examination is carried out on an empty stomach, which has usually been previously aspirated, reduces the danger of peritoneal soiling to a minimum. This is perhaps the most important factor in influencing the type of treatment carried out. Schindler feels that, under these circumstances, perforation is not an exceedingly dangerous event and that the danger of conservative treatment, if feeding is avoided for

a few days, is not greater than with surgery. Further clinical experience is needed to crystallize our views on this aspect of the problem.

It is noteworthy that in recent years a place is being accorded to the conservative management of perforated peptic ulcer. Wangensteen<sup>3</sup> deals with the *formes frustes* as a definite entity and mentions as factors in the conservative management, delay in operation, size of the perforation, status of the digestion at the time of operation and general physical condition. Great emphasis is placed upon immediate suction.

#### SUMMARY

A case of apparent rupture of the stomach and pneumoperitoneum is reported. Laparotomy three hours later revealed an intact stomach.

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## EDITORIALS

### PRESENTATION OF FRIEDENWALD MEDAL TO FRANKLIN W. WHITE

APRIL 30, 1948

It is a unique pleasure and privilege to pay tribute this evening to one of our most distinguished and admired members.

Before commenting upon Franklin White's interesting biography and his 80 published contributions to internal medicine and gastroenterology, I should like, first, to refer to him as the friend and colleague whom we have known in this Association. In retrospect, we all have a most pleasant memory of the role he has played in our deliberations. His keen intellect and fine critical sense, his progressive spirit and numerous, stimulating contributions to our meetings and to the literature, his consideration for the feelings of others, the twinkle in his eye and his keen sense of humor have made him not only one of our most eminent members but also an outstanding personal favorite among us. For him we have the greatest respect, admiration and affection.

During the 40 years he has been a member of this Association, Dr. White has been a stimulating leader and a leavening influence. On certain occasions in meetings he has called attention to the occasional questionable statements of fellow members, but he has such a delightfully subtle manner of partially concealing his constructive criticism in the form of a searching question, that he never hurts the man he is trying to help. That is the reason he has helped so many of us.

Franklin White's biography is of interest. He was born in Boston on October 23, 1869. I shall not attempt to trace his boyhood, although there must have been few dull moments in it. He obtained his B.S. degree in Biology from the Massachusetts Institute of Technology and his M.D. degree from the Harvard Medical School. He was a house officer and held the Dalton Fellowship at the Massachusetts General Hospital. In his early years he taught bacteriology and conducted research in this field. For the last 40 years he has been teaching clinical medicine as a member of the faculty of the Harvard Medical School, and for 33 years has been a valued member of the staff of the Boston City Hospital.

Dr. White has been honored by being elected Secretary and, later, in 1927, President of this Association. He also has been Secretary and subsequently Chairman of the Section of Gastroenterology of the American Medical Association. He has been a former Regent of the American College of Physicians



FRANKLIN W. WHITE

and a member of the American Roentgen-Ray Society. He is one of the small group of members of this Association to be specially honored by election to membership many years ago in the Association of American Physicians.

The medical publications of Dr. White first appear in the literature in 1908. During the subsequent 40 years he has published a total of 80 medical articles dealing with a wide range of subjects. His first eleven publications relate to various phases of bacteriology and internal medicine. The subsequent 69 publications all deal with various phases of gastroenterology.

It is not possible on this occasion to attempt any detailed discussion of the individual contributions Dr. White has made to our knowledge of gastroenterology. His publications cover the entire field. All of his writings portray painstaking observations and keen interpretation, a progressive spirit in evaluating new methods but marked conservatism in his deductions. His early writings include classical studies of achylia gastrica and acute yellow atrophy, an early evaluation of the significance of occult blood in the stools, studies upon pyloric obstruction and the clinical results of gastroenterostomy, an appraisal of the value of Roentgen Ray studies in the diagnosis of gastric and duodenal ulcer and of early gastric carcinoma, with a notation of the limitations, an evaluation of the advantages and difficulties of non-surgical biliary drainage and many other subjects.

Dr. White's later contributions have included improvements in the treatment of peptic ulcer, observations upon the healing of gastric ulcer, studies of tumors of the small intestine, an appraisal of gallbladder disease, and more recently his exhaustive studies of jaundice and his evaluation of liver function tests. He has contributed chapters to both Tice's and Nelson's Systems of Medicine. We shall not soon forget his latest contribution of one year ago, when he outlined in a fascinating manner the history of this Association from its inception in 1897 up to the time of our fiftieth anniversary last year.

It affords us all profound satisfaction to present the Friedenwald Medal, the highest honor this Association can confer upon any member, to a distinguished clinician, an effective teacher and a notable contributor to our knowledge of gastroenterology, an invaluable colleague in this Association, and a rare type of friend, Franklin Warren White.

JOHN G. MATEER

## WILLIAM PROUT, THE DISCOVERER OF HYDROCHLORIC ACID IN THE GASTRIC JUICE

Last year Dr. Anthony M. Kasich, in the July, 1946, number of the *Bulletin of the History of Medicine*, presented an interesting article on William Prout, the discoverer of hydrochloric acid in the gastric juice. A number of previous workers had noticed that the gastric juice was acid, but in the then state of chemical knowledge it is not surprising that no one learned what the acid was.

William Prout was born in England in 1785. He was a precocious child who read everything he could lay his hands on, and was particularly fond of natural history. At the University of Edinburgh he fortunately fell under the influence of one of the most distinguished chemists of that day, and for the rest of his life he was more interested in chemistry than in medicine. After graduation he settled in London and continued to study and practice medicine, but before long he was lecturing to select audiences on chemistry. Eventually he became the leading chemist of his country.

In 1815 he published anonymously a paper, "On the relation between the Specific Gravities of bodies in the gaseous state and their Atoms." It was a remarkable work for a young man of twenty-eight, or for anyone, since it stated that there are good grounds for believing that the atomic weights of all elements are exact multiples of the atomic weight of hydrogen.

On December 11th, 1823, before the Royal Society of London, Prout read a paper "On the Nature of the saline Matters usually existing in the stomachs of Animals." In that paper he stated that the acid was muriatic. He proved this for the stomach of the hare, the horse, the calf and the dog. He also found free muriatic acid in great abundance in the acid fluid from the human stomach in cases of severe dyspepsia. It is possible that at times he removed this fluid with a stomach tube, because such tubes were available in that day.

Remarkable was Prout's statement that the source of the muriatic acid must be the common salt existing in the blood. As he said, this must dissociate, the chlorine going into the gastric juice and the sodium remaining behind in the blood, there to add to the slight alkalinity of this fluid. Part of it, he saw, would be excreted into the bowel, there to neutralize the acid coming down into the duodenum. And even more remarkable was his ability to see that electrical forces had to do with this dissociation.

Although some subsequent workers confirmed Prout's findings, Lauret and Lassaigne, in 1825, maintained that Prout was wrong and that gastric juice contained lactic acid. Unfortunately, for years this false view was accepted by writers of textbooks, and even as late as 1894, one can find in Bury's Clinical Medicine the statement that in health the gastric juice contains lactic acid.

Eventually, however, as usually happens, the truth won out, and Prout was given the honors due him, such as the Copley Medal, election to Fellowship in the Royal College of Physicians, and appointment as Gulstonian Lecturer. But he was too far out ahead of his time, and as always happens to men in this position, he ran into a lot of criticism and persecution. He saw clearly that most of physiology and much of medicine could best be explained on a chemical basis, but in this view he ran afoul of the so-called vitalists, who maintained that chemistry had nothing to do with it and it was all due to "vital functions," whatever those were. Prout was willing to use this term and to ascribe to the idea some value, but he saw its limitations. It was not until some seventy-five years later that Jacques Loeb was able to convince all open-minded scientists that much of what in insects and animals passes for intelligent behavior is really only a blind and reflex reaction to chemical substances or to light or gravity or touch. A butterfly soars when certain bodily secretions make it heliotropic and goes back to earth when its secretions make it geotropic.

Eventually Prout died and, as Reiter said in 1850, were it the custom of nations to bestow honors on those who bring great gifts of healing to their fellowmen, Prout's name would have been one of the greatest in the roll of Great Britain's gifted sons. But seeing that a nation's greatest honors are reserved for those who are most skilled in the destruction of human life or in the devious ways of the politician, the man who did so much to lay the foundations of modern physiology died almost unnoticed.

W. C. A.

## COMMENT

### THE CAUSES OF SUDDEN DEATH IN YOUNG MEN

In these days of ever-widening interest in diseases of the blood vessels, particularly in younger men and women, the paper of Moritz and Zamcheck<sup>1</sup> on sudden and unexpected deaths of young soldiers is well worth reading. They reviewed the results of necropsies made in the cases of 1,000 apparently healthy soldiers who had died suddenly. Their ages ranged from eighteen to forty years. The most common diseases encountered were cardiac troubles, intracranial hemorrhages and meningitis. There were 350 sudden deaths from previously unrecognized disease of the heart, and approximately 300 of these deaths were due to sclerosis of a coronary artery. Eight per cent of the patients with this disease were under twenty-five years of age, and twenty-two per cent were younger than thirty years of age. Many of these soldiers died during strenuous physical exercise. Fewer than one in four had any history suggesting cardiac embarrassment before death. The necropsies in these cases showed in every case severe atherosclerosis of one or both coronary arteries. In most of the cases the fatal thrombus had apparently been forming for hours or days before it produced death.

In sixty-nine of ninety-one cases reviewed, the sudden death was due to intracranial hemorrhage, and the point of rupture was probably in one of those tiny aneurysms which are often found in the circle of Willis. Some 20 per cent of the soldiers with this trouble had had some headache.

In 110, or about a third of all reported cases of death due to infection with meningococci, the exitus occurred within twenty-four hours after the onset of incapacitating symptoms. More than half of the patients were dead within six hours after they reported ill! In perhaps 70 per cent of the cases the soldier had been feeling below par or had thought he had a mild cold shortly before he became severely ill and died. In 71 per cent of these cases there was focal or massive hemorrhage into the adrenal glands. The impression gained was that before this hemorrhage took place there were degenerative changes in the cells of the cortex.

Curious is the fact that in at least 140 of the cases in which a careful necropsy was made, the pathologist couldn't find any anatomic abnormality to explain the death. Perhaps as Dr. H. E. Robertson often used to say, the patient died a physiologic death; in other words, something went so severely wrong with the chemical processes in some organ that life ceased.

W. C. A.

#### REFERENCE

<sup>1</sup> MORITZ, A. R., AND ZAMCHECK, NORMAN: Sudden and unexpected deaths of young soldiers; diseases responsible for such deaths during World War II. Arch. Path., 42: 459-494 (Nov. 1946).

## THE DANGER OF GIVING LARGE AMOUNTS OF VITAMIN D

For years, now, on questionable evidence, many physicians have been prescribing huge doses of vitamin D with the idea of curing arthritis. Experts in this field of medicine doubt if it does any good but they are sure that occasionally it does great harm.

There are cases in which the patient slips into a condition which resembles diabetes insipidus with polydipsia, polyuria, and a high blood calcium. One distressing feature of these cases is that stoppage of the medication does not, for months, make much change in the situation. In other cases the kidneys will suddenly fill up with stones.

In the December 1947 number of the *American Journal of the Medical Sciences* there is a paper by Frost, Sunderman and Leopold who show that prolonged hypercalcemia can give rise to a serious calcareous infiltration of the sclera, the conjunctiva and the cornea of the eye. These authors reviewed some of the literature, which shows that vitamin D can seriously injure renal function, producing albuminuria, hematuria and the retention of nonprotein nitrogen. Certainly the kidneys and their function should be watched carefully whenever huge doses of vitamin D are given.

Interesting, also, is the fact that calcification can take place in the soft tissues round the groins. There can also be marked calcification in the arterial system and the kidneys. It should never be forgotten, also, that animals can be killed by the giving of large doses of irradiated steroids.

One difficulty with the use of vitamin D is that there is a marked difference in the amount of the drug that will produce disease and injury in different individuals. It appears to be particularly dangerous to give large amounts of calcium together with the vitamin D, as is done sometimes when an orthopedist wants to help the healing of a fracture.

In the case reported by Frost, Sunderman and Leopold there came a marked hypercalcemia which was still present eight months after the patient had stopped taking vitamin D. This persistence of the harm that is done adds greatly to the danger of using the drug. There is one report of a case in which the hypercalcemia was still present a year and a half after discontinuance of the treatment.

Certainly a patient should never be turned loose to treat himself as long as he wants with huge doses of vitamin D. His condition should be watched.

It is unfortunate that some vendors of vitamin D have gone out of their way trying to convince physicians that the use of the drug in huge doses is perfectly safe. Certainly any physician who has ever seen a few cases of serious injury due to the use of vitamin D will not subscribe to that statement.

It is unfortunate, but throughout the long history of medicine, one finds that

physicians have always had so much pressure put upon them to do something for the person who is desperate because of the persistence of some disabling disease that always they have used in large quantities drugs the usefulness of which has never been demonstrated. Today any physician past sixty years of age can remember the time when everyone with a cough or with tuberculosis had his or her digestion ruined with large doses of creosote which was supposed to kill the offending bacteria, but didn't.

Doubtless, physicians will always be high-pressured into giving drugs whose usefulness has never been demonstrated scientifically, but in that case the wise man who does not want to do harm will prescribe small doses.

W. C. A.

## BOOK REVIEWS

THE ENGRAMMES OF PSYCHIATRY. *J. M. Nielsen and George N. Thompson.* C. C. Thomas. Springfield, Illinois, 1947, p. 509, price \$6.75.

The authors believe that impulses traveling over neuronal engrammes are the basis of each and every cerebral function and that the anatomy and physiology of the mind are simply the anatomy and physiology of the cerebral engrammes. By engrammes the authors apparently mean pathways worn through the brain by repeated use. They believe that a knowledge of the anatomy and physiology of the brain would be the only true basis for an understanding of mental disturbances. This may well be true but it's questionable if our knowledge of the brain is ready yet to carry this big burden. It is rather typical of the psychology of many psychiatrists today that Nielsen and Thompson used for their title a word which practically no one has ever heard of before. On turning to the medical dictionary one finds a definition which is not the one that these authors apparently use, but actually they do not define the word carefully as they should have done in the preface.

Nielsen and Thompson have had a wide experience with psychopathic personalities, especially in the department of correction of the state of California, and probably the best chapter in the book is on the psychopathic personality. Every physician would do well to read it. One finds there described the type of odd person who can be very ingratiating and who easily makes devoted friends who are willing even to take him into the home in an effort to rehabilitate him. Unfortunately, within a few weeks or months he turns savagely on the benefactor for some slight supposed affront and curses him roundly. As a result the psychopath is out on the street and broke again. Such persons take everything as if it were their due and never show any sign of appreciation. They are intensely selfish. There is no gratitude in them and they never change or reform. They cannot be rehabilitated.

Incidentally, it's comforting to find in this book repeated statements to the effect that certain types of psychopath are incurable. Some constant lawbreakers seem unable to look ahead to see that what they do impulsively is bound soon to bring punishment and great trouble. If asked why they did some foolish thing they say, "Because I wanted to," and that is sufficient explanation for them just as it is for a naughty child.

Interesting is the statement of Nielsen and Thompson that in their opinion the psychoneurotic very rarely loses his mind or gets a psychosis. Interesting also is the fact that many a psychotic is an excellent workman and is prized by his employers until someday he blows up about some little thing and shows that he is not sane. For instance, one of the best research chemists in a big plant went to the president of the company and said, "See here, you have been annoying me by changing labels on my bottles; I've had enough, and the next time you do it I'll put a bullet between your eyes!"

There is much in this book that will not be of great interest to the non-psychiatric

physician but there is a great deal that he should read and can be read with pleasure and profit.

PATOLOGIA DIGESTIVA, ACTUALIDADES, CLINICO-RADIOLOGICAS Y TERAPEUTICAS, Vol. II. *B. Varela Fuentes and A. Munilla and twenty-eight contributors.* Espasa-Calpe. Argentina, S. A., Buenos Aires, pp. 782, 1947.

This is an ambitious work, well-written, printed and illustrated and documented. Every Spanish speaking gastroenterologist will want to have a copy on his desk. There are chapters on constipation, the radiologic study of the terminal ileum and the ileocecal sphincter, amebiasis, chronic ulcerative colitis, cholecystography, congenital malformations of the biliary tract and hydatid disease of the liver, cirrhosis of the liver in the child, obstruction of the cystic duct, a study of the metabolism of the biliary pigments, anemia with falciform red blood cells, experimental pancreatitis, alcaptonuria, and two chapters on certain phases of diabetes.

The treatment of chronic ulcerative colitis is that used in the United States today. In this disease penicillin appears to be of value mainly for the clearing up of complicating inflammations. A curious chapter is one on the treatment of gastroduodenal ulcer with female sex hormones. There is a good chapter based on research as to the innervation of the digestive tract. Another unusual chapter is on intraabdominal pressure, and another is on the innervation of the liver and the biliary tract. There is an unusual chapter on xanthomatosis with cirrhosis of the liver. This appears to be a common condition in the Argentine.

KOMPENDIUM DER PARASITISCHEN WURMER IM MENSCHEN. *Hans A. Kreis.* Benno Schwabe & Co. Basel, Switzerland, 136 pages, 1947, price Fr. 10.-

This is an attractive little book on the parasitic worms of man. In the introduction it is stated that the writer had a large experience in this field. In the case of each worm the several treatments with different drugs are described. One cannot help wishing that the author had given more details from his own experience. For instance, after a physician has failed a few times in attempts to rid a child or an adult of round worms or thread worms what is he to do next. Also, is there any real danger to the liver in giving children large doses of anthelmintics?

RADIUM DOSAGE, THE MANCHESTER SYSTEM. *Edited by W. J. Meredith.* The Williams & Wilkins Company. Baltimore.

The pioneers in therapeutic radiology were forced to treat rather empirically, according to results achieved, and depending on clinical experience. The formulation of the roentgen as a unit of dosage, and late correlation of the x-ray roentgen with the gamma roentgen, has placed x-ray and radium therapy on a scientific foundation. While clinical experience still is a very important factor in dosage determination, the radiologist beginning practice must depend on collaboration with the physicist, and in fact, must absorb some physics himself, however painful the process. The Paterson and Parker tables, published in the 1930's, have become indispensable for beginners in radium therapy. The essential tables and several by other English authorities have

been brought together in the excellent book "Radium Dosage, The Manchester System", edited by W. J. Meredith of the Christie Hospital and Holt Radium Institute, and published in this country by the Williams and Wilkins Company of Baltimore.

The text is divided into two parts; the first entitled Clinical Aspects, and the second part Physical Aspects. The appendix contains tables to figure radium dosage for every conceivable type of applicator, whether the radium is mounted on or in molds or cylinders or implanted in tissues, and correction is given for variation in the filter used. One thousand roentgens have been chosen as the clinical working unit, and the tables enable one to calculate the milligram hours required to produce one thousand roentgens in any given situation.

An interesting chapter discussed a system of dosage for a lesion offering complex problems to the physicist, that of cancer of the cervix. Figuring the dosage in roentgen is extremely difficult here because of the variation in the size and shape of these cancers, and of the different applicators employed in treatment.

While there is no discussion of biologic effects of irradiation in this book, the more neglected field of radiation physics is splendidly handled. In short, this book supplies a real need, especially for the radiologist commencing the practice of radium therapy.

METHODS OF DIAGNOSIS. *Logan Clendenning and E. H. Haslinger.* C. V. Mosby Company. St. Louis. 1947, 868 pp. \$12.50.

In reviewing a book like this one wonders immediately if it is enough different from others and is it enough more interestingly written or filled with information so that there should be a place for it. One would expect anything that Clendenning had to do with to be more than usually interesting. With his vivid personality he could hardly write dully. He also had many many years back of him of teaching.

Right at the beginning one discovers something which obviously should be in every textbook of diagnosis and which probably never has been included in one, and that is a chapter on logic. If ever there was a man who needed a good knowledge of logic in his daily work it is the diagnostician, and yet, in medical schools, no course is given on the subject.

On page 59 is an interesting story told Clendenning by the late Le Roy Crummer. Crummer related how for years his blood chemistry work was done by a young woman. One day Mrs. Crummer gave her a sample of silk to match at a downtown store. She thought that a girl who spent most of her day matching colors in a colorimeter should be ideal for matching the piece of silk. Actually the girl returned with a piece of goods that was away off in color; the girl was partially color-blind. Crummer then wondered how far off must have been many of the reports she had been turning in to him through the years.

Clendenning remarked on how important to the physician is knowledge of physical diagnosis, and hence he went into that phase of the subject with more than usual thoroughness.

As he said, a patient doesn't come in saying that I have amyotrophic lateral sclerosis or typhus fever. He says, "I'm dizzy," or, "I've lost weight," or "I have a

pain." Many textbooks of medicine take up the description of one disease after the other but Clendenning thought it best to start with symptoms and signs and then go on with laboratory tests, roentgenologic and electrocardiographic studies, etc.

Helpful are the many references to the literature.

This is a good book and a good addition to any physician's library.

**SEXUAL BEHAVIOR IN THE HUMAN MALE.** *A. C. Kinsey, W. B. Pomeroy, and C. E. Martin.* W. B. Saunders and Co. Philadelphia, 1948, pp. 804.

This is an epoch making book and one that should interest all scientists, physicians, sociologists, legislators and jurists.

It is a curious fact that even physicians as a class are prudish, with many strongly averse to permitting anyone to make a scientific study of sex in man. It's all right to study sex in animals, but not in man. As a result of this prejudice and refusal to face facts that might be unpleasant, no one has ever yet been able to make an adequate study of sex, and in this country there has been no center where such studies could be carried out. In the last few years several helpful studies have been made of the sex lives of men and women, but they were far from adequate.

Some years ago, Doctor Kinsey, professor of Zoology at the University of Indiana, got to wondering why he couldn't find answers to some of the questions his students asked him about sex in man. He went to several universities trying in vain to find someone who had studied the subject. Finally he went to Doctor Gregg of the Rockefeller Foundation to ask him if he knew of any studies being made anywhere. Gregg wisely said, "Why don't you make the study yourself" and offered to supply the necessary funds for a research center.

Since then Kinsey has been gathering information with the same scientific detachment which he used for years in studying the sexual life of the insects which were his main interest. He realized immediately that in order to get material of value the questionnaire could not be used. He would have to interview a fairly large sample of the populace. Like the expert takers of polls, he'd have to be careful to sample all types of men and women in all levels of society. He would have to question the educated and the uneducated and negroes as well as whites; he would have to question the lady in the drawing room, her maid in the kitchen, and the prostitute in the roadhouse.

Before he could get truthful answers he would have to convince people that in no way could the information given over get into the hands of others, and its source be identified. In order to insure such secrecy the notes Kinsey and his associates make are only checks in little compartments on an unidentifiable piece of paper that has no writing on it. Next the people interviewed had to be convinced that Kinsey's curiosity was purely scientific and that no matter what was told him he wouldn't blame or be shocked or raise his eyebrows. He would not care one whit whether in certain circles a certain behavior was looked on as right or wrong; all he would want to know was what the man or woman had done. Kinsey had to be the sort of man whom people could trust, and be willing to talk to, and actually he is the type of man whom one immediately trusts and likes.

He soon trained two associates, Pomeroy and Martin, who are helping him with

the interviewing of subjects. This book is the first of several volumes that are planned. This one deals with the sex life of 5,300 white males.

It is first a report of what boys and men do in a sexual way: it raises no questions as to what they should do or as to whether what they do is right or wrong or good or bad for them or for society. Kinsey and his co-workers have already shown that much of what has been accepted as being normal sexual behavior is not that at all. As they say, in no other field of knowledge have scientists been satisfied to accept the standards of normal as set up without any research by sex-hating monks, theologians, mystics and jurists who lived two or three thousands years ago.

In a brief review like this, one cannot go into details about the results obtained so far. All that can be said is that this study has revealed many remarkable facts which will bring surprise to many. Particularly surprising to the reviewer was the discovery of how common homosexualism is among males, also the richness of the sexual life of unmarried youths, high school students and even grammar school students. Astounding is the amount of intercourse with animals on the farm, and astounding is the difference between the sexual habits and ideas of the man who does not go beyond grammar school and the man who goes on through college.

It is to be hoped that some day these remarkable discoveries will have some influence on our laws and the way they are administered. Some day those who make our laws will have to face the facts of life as Kinsey reveals them. If everyone who today commits adultery or sodomy were put in jail as the laws direct, civilization would come to a sudden stop with most of the populace in states' prison and the rest guarding them and feeding them!

AN INTRODUCTION TO GASTROENTEROLOGY, A CLINICAL STUDY OF THE STRUCTURE AND FUNCTIONS OF THE HUMAN ALIMENTARY TUBE. *James D. Lickley.* Williams & Wilkins. Baltimore, 1947, pp. 143.

It is practically impossible to write an Introduction to Gastroenterology in 143 pages; one might perhaps do an adequate job with 1,400. About the only way in which to make a little book like this of value is to cram it with thoroughly boiled-down information, and information which is most carefully chosen and as accurate as modern research can make it.

By these standards this little book fails; the material was not chosen well enough and it is not concentrated enough. Probably because the writer was once a demonstrator of anatomy, the first thirty-four pages on the structure of the digestive tube are the best.

# ABSTRACTS OF CURRENT LITERATURE

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## MOUTH AND ESOPHAGUS

HALPERT, B. AND TOOL, C. D. Anlage tumors of the salivary glands. *Cancer Res.*, 7: 346 (June) 1947.

The cellular structures of anlage tumors occurring in the salivary glands were studied in 38 patients. In 29, the growth occurred in or about the parotid glands; in 6, about the submandibular glands; and in 3, in the maxilla. There was no fundamental difference in the gross appearance or microscopic structure between the growths arising in the parotid regions and those situated elsewhere. The sites of origin and their structural patterns suggest that they are derived from embryonal rests of the ectoderm. The structural differences may be attributed partly to influences of the environment on the tumors in their respective sites, and in part to the stage of evolution of the cell rests at the time of separation from the ectodermal anlage. The salivary gland tumors appear to be the oldest genetically. The group of cells from which they originate

must have separated from the ectoderm at the stage when they had as yet not acquired their dominant characteristics as ectodermal and mesodermal cells; hence, their capacity to differentiate into ectodermal and mesodermal tissues.

JOSEPH B. KIRSNER.

LONGMIRE, W. P., JR. Congenital atresia and tracheoesophageal fistula. *Arch. Surg.*, 55: 330 (Sept.) 1947. The most common congenital anomaly of the esophagus is complete atresia; the upper segment ends in a blind pouch and the lower segment communicates with the trachea near the bifurcation. The most important step in the management of these cases is the early recognition of the anomaly before the infant's life is seriously threatened by aspiration pneumonia or dehydration and starvation.

Four consecutive patients with tracheoesophageal fistula and esophageal atresia, who have survived ligation of the fistula and

primary anastomosis of the esophagus, are reported together with the operative technique.

C. WILMER WIRTS, JR.

### STOMACH

CRANDELL, W. B., BOEHM, W. E., AND MULHOLLAND, J. H. Effects of supra-diaphragmatic section of the vagus nerves in man. *Arch. Surg.*, 55: 343 (Sept.) 1947.

The secretion of gastric acid in response to alcohol administered intravenously and intragastrically appears to be diminished after section of the vagus nerve. This operation does not appear to change the electroencephalographic pattern of patients with peptic ulcer, nor impair their utilization and absorption of protein as indicated by nitrogen balance studies. The usual diminished gastric motility has been found clinically and roentgenologically.

C. WILMER WIRTS, JR.

GUZZETTA, P. C., JR. AND SOUTHWICK, H. W. Acute phlegmonous gastritis. *Surgery*, 22: 453 (Sept.) 1947.

Acute phlegmonous gastritis has been described as a carbuncle or erysipelas of the stomach. It is a nonspecific infection of the stomach wall characterized by seropurulent or fibrinopurulent inflammation usually involving all the gastric layers to some extent but affecting chiefly the submucosa. The offending organism is over 70 per cent hemolytic streptococcus, but many other organisms have been encountered. It may arise as a local condition especially where there is hypoacidity but usually is believed to be metastatic. The signs and symptoms are those of an acute lesion of the upper abdomen, plus sepsis. The epigastric pain is sudden, severe, continuous, well localized, not referred to the back and may be relieved when the patient sits up. Vomiting is usual but pus in the vomitus is rare. Correct preoperative diagnosis is rarely made, the disease being confused with perforated peptic ulcer, acute pancreatitis, acute cholecystitis, cholelithiasis, and basal pneumonia. The best treatment is probably gastrotomy, with incision and drainage of the stomach cavity

and closure of the gastrotomy—combined with penicillin and sulfadiazine. One successfully treated case is reported.

J. DUFFY HANCOCK.

### BOWEL

PULASKI, E. J. AND AMSPACHER, W. H. Streptomycin therapy for certain infections of intestinal origin. *New Eng. J. Med.*, 237: 419 (Sept.) 1947.

Streptomycin was used in the treatment of 12 acute and 13 chronic cases of brucellosis. The overall results, whether the dosage was small or large, were poor. Bacteremia disappeared in some of the acute cases, but recurrences were frequent. Symptomatic relief may have been due to expected natural remissions and to psychologic factors rather than to streptomycin. The fact that streptomycin is poorly absorbed from the gastrointestinal tract and is not inactivated by the bowel contents suggests that its oral use in certain susceptible infections is logical and useful. The administration of 4 g. daily by mouth causes 0.01-0.02 g. per gram of feces to appear in the stools and rapidly eliminates gram negative bacteria from the bowel.

Results in 6 cases of acute typhoid fever were disappointing. In only one case could streptomycin be credited with a cure. In 2 typhoid carriers, streptomycin failed to eliminate typhoid bacilli from the stool. In one case of paratyphoid, streptomycin administration was followed by prompt recovery. Ten cases of bacillary dysentery were treated, and in every case the results were good to excellent. The causative bacilli disappeared from the feces and symptomatic improvement was concomitant. In 10 cases of enteric infections with *Salmonella* organisms, combined oral and intramuscular therapy for 7 days eliminated the organisms from the blood stream and feces with relief of symptoms. There were no relapses. Sixteen cases of ulcerative colitis were treated with streptomycin. The majority derived some benefit during treatment but the overall findings were contradictory and no particular optimism seems warranted. Among 13 infants with epidemic diarrhea that were treated, there

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were 2 deaths. Results were usually good and sometimes dramatic. The authors conclude that in infections caused by organisms susceptible to streptomycin the results are likely to be good if the drug can be brought into contact with all of the foci of infection. However, if the organisms are not susceptible to streptomycin, treatment is without value.

ANTHONY M. KASICH.

GUPTILL, P. Familial polyposis of the colon. *Surgery*, 22: 286 (Aug.) 1947. In familial polyposis of the colon, the pathological proliferation of the epithelial lining may occur as villous, sessile, or pedunculated structures. It occurs in families and progresses to malignant degeneration in a high percentage of cases. The direct causative factor is unknown but it behaves as a Mendelian recessive and is transmitted by genes. The indirect or precipitating cause plays a small share. The disease may assist at birth—a well developed case having been seen in a two-year old child. To the group of 347 cases previously reported, five cases seen in two families are added. Diagnosis is made from history, digital examination of the rectum, proctoscopy, X-ray of the colon by contrast enema, and air replacement enema. The most desirable surgical treatment at present consists in fulguration of the polyps in the lower rectum, anastomosis of ileum to rectum, a two-stage colectomy, and subsequent close observation of the remaining rectal segment which should be sufficiently short to be readily accessible to direct vision and easy fulguration. X-ray treatment is ineffective.

J. DUFFY HANCOCK.

SMITH, H. G. AND KREDEL, F. E. Localized acquired megacolon treated by sympathectomy. *Surgery*, 22: 259 (Aug.) 1947.

True megacolon or Hirschsprung's disease is seen in infants and children and represents a congenital dilatation of the colon of neurogenic origin. Acquired or pseudo-megacolon occurs in adults usually secondary to chronic obstruction from various organic causes, although some of the cases included

show no such organic obstruction. While many cases of Hirschsprung's disease have been treated by some form of sympathetic denervation of the colon, segmental resection or total colectomy has recently been advocated. In the acquired type, direct surgical attack on the underlying cause is the method of choice. In some cases anatomical factors may prevent this type of attack and in others no demonstrable organic lesion may be found. Three such cases are reported. Satisfactory results were obtained by a combined presacral, preaortic, and inferior mesenteric neurectomy.

J. DUFFY HANCOCK.

HOXWORTH, P. I. AND MITHOEFER, J. Management of cancer of the colon. *Surgery*, 22: 271 (Aug.) 1947.

The general principles for the treatment of cancer of the colon include resection of the bowel wide of the original growth, removal of an extensive area of the regional mesentery and lymphatic structures, and preservation of an adequate blood supply to the remaining segments of colon. Re-establishment of the continuity of the bowel may be by delayed or immediate anastomosis. If safety can be established, the authors prefer the immediate method because of greater postoperative comfort, avoidance of interval colostomy, freedom from secondary operative procedures, and shortened cheaper hospitalization. To establish safety, cases distal to the hepatic flexure and showing obstruction are given a preliminary colostomy or cecostomy. In the rare case of obstruction due to lesions in the cecum and ascending colon, relief may be obtained by continuous gastric suction, use of the Miller-Abbott tube, or ileotranverse colostomy. Other pre-operative measures include supportive transfusions, high caloric low residue diet, correct vitamin intake, thorough cleansing of the bowel, and succinylsulfathiazole. Operative technique is well described and beautifully illustrated. Gentleness and careful hemostasis are emphasized. Postoperative care includes glucose and saline intravenously with the substitution of whole blood where indicated, and sulfadiazine and penicillin parenterally for any questionable soiling or

suggestive sepsis. Operative data and results are given.

J. DUFFY HANCOCK.

PORGES, O. The jejunal syndrome. Am. J. Med., 3: 177 (Aug.) 1947.

The so-called "dumping" syndrome observed in patients after gastric resection is better titled "jejunal syndrome". It is frequently due to severe enteritis or jejunitis and is observed in the absence of gastrectomy. Clinically, the patients become tired and sleepy after meals, followed by nausea, epigastric pressure, heat sensations and sweating. Where tachycardia, hypotension and syncope occur, the nomenclature suggested is "jejunal shock". The physical findings in enteritis reveal tenderness of the left abdomen at the level of the umbilicus, whereas in ileitis the tender pressure point is to the right of the umbilicus. The most important test for the diagnosis of enteritis is the microscopic examination of the feces which will disclose numerous soaps as crystals in the form of blunt needles, sometimes along with slender needles of fatty acids. Roentgen examination reveals accelerated motility of a barium meal.

The "jejunal syndrome" is rare while enteritis is a rather common disease. In the majority of cases the distress is not severe, and there are many instances with no complaints. The disease is of greater importance because of the complications and sequelae of diarrhea, flatulence and infection. A case report illustrates an example of a "dumping" syndrome without dumping, in a male of forty-three with acute enterocolitis.

MICHAEL W. SHUTKIN.

METZ, A. R. Duodenal regurgitation. Arch. Surg., 55: 239 (Sept.) 1947.

Duodenal regurgitation should be suspected in recurring attacks of nausea and vomiting associated with weight loss. The positive diagnosis is made by the radiologist on the observation of a dilated duodenum to the right of the spine, with delay of the barium passing over the spine and with hyperperistalsis and regurgitation of the barium back into the stomach. Medical manage-

ment should be tried but if satisfactory results are not obtained in 1-2 months, a duodenojjunostomy or gastroenterostomy with occlusion of the pylorus by ligation should be advised.

C. WILMER WIRTS, JR.

EHRLICH, R. Pathogenesis and treatment of ulcerative colitis with extract of hog stomach. Am. J. Dig. Dis., 14: 294 (Sept.) 1947.

While recognizing that ulcerative colitis is usually a non-specific disease, the author hypothesizes upon the possibility that dissolution of the colonic mucosa, and subsequent invasion by various organisms, may be the result of the presence in the lower bowel of excessive quantities of proteolytic enzymes. He believes that this may result from marked gastrointestinal hypermotility which results in the delivery of active proteolytic enzymes from the upper gastrointestinal tract and pancreas into the colon, thus leading to a disturbance of the usual proteolytic, anti-proteolytic enzymatic balance.

Because of the belief that dessicated extract of hog stomach contains a good bit of anti-proteolytic substance, this material was used in the therapy of ulcerative colitis. The author reports upon results of its administration by mouth in 15 cases of idiopathic ulcerative colitis, usually in doses of 30-60 grams daily. In 4 of the cases, it was believed advisable to give sulfonamide therapy for secondary infections. The administration of the hog stomach seemed to be followed by rapid restoration of the mucosa to an intact state, and its use is recommended as being a more specific approach to the general therapy of ulcerative colitis.

HENRY TUMEN.

SHRAPNEL, B. C. Oral emetine in the treatment of intestinal amebiasis. Am. J. Trop. Med., 27: 527 (Sept.) 1947.

Five children and 25 adults were treated with emetine hydrochloride administered in enteric-coated tablets. The cases included the acute, chronic, and carrier types. The children were given  $\frac{1}{2}$  grain three times a day for 12 days; the adults received double

this dose. No toxic manifestations as nausea or vomiting were encountered. One of the children also received blood transfusions and sulfaguanidine. All cases were clinically cured with a single course. In one case, however, trophozoites were found in the stool 7 months after treatment. The results show the efficacy of emetine administered enterally. The drug may also be useful against *Trichuris trichiura* (whipworm).

PHILIP LEVITSKY.

VAN GELDEREN, C. Über die chirurgische Behandlung des idiopathischen Megacolons (der Hirschsprung'schen Krankheit). [Surgical treatment of idiopathic megacolon (Hirschprung's disease).] Arch. Chir. Scand., 94: 81 (June) 1946.

Idiopathic megacolon is considered from the clinical, pathological and etiological points of view. Extensive sympathectomy is the treatment of choice to-day.

PHILIP LEVITSKY.

FARRIS, J. M. AND ROMACK, H. H. The effect of streptomycin in "closed-loop" appendicitis. An experimental study. Surgery, 22: 305 (Aug.) 1947.

Appendiceal exudates in man contain *B. coli* in 85 per cent of cases, and in over 60 per cent the gram negative colon group is predominant. A drug acting primarily on gram-negative organisms (streptomycin) should offer advantages over drugs acting primarily on gram-positive organisms (sulfonamides and penicillin). Thirty young adult rabbits were used. In all, the appendix was crushed and ligated at its base to accomplish an obstructive "closed-loop" appendicitis. All appendices were distended with sterile lipiodol or 70 per cent diodrast. Ten animals were used for control; 9 were dead in less than 40 hours. In 10 other animals, a single local injection of streptomycin was placed in the lumen of the appendix after devascularization. The other 10 animals were given streptomycin parenterally but not locally. Nineteen of these 20 streptomycin-treated animals survived. The one fatality was apparently an operative death due to faulty technique. The rabbits receiving streptomycin locally

seemed to improve more quickly and smoothly than those receiving the drug parenterally. Apparently bacteriological aspects of closed-loop intestinal obstruction are more important than mechanical factors and other allied theories relative to the concomitant "toxemia".

J. DUFFY HANCOCK.

BRUUSGAARD, C. Volvulus of the sigmoid colon and its treatment. Surgery, 22: 466 (Sept.) 1947.

Volvulus means tortion of the bowel on its mesentery, causing symptoms due to narrowing of the bowel, strangulation of its blood vessels or both. It may be acute, subacute, or chronic. A mechanical ileus results in most cases. In the history there are usually passing attacks of abdominal pain, increasing constipation, possibly bloody stools with a foul odor, and increasing gaseous distention. The upper abdomen shows balloon type distention. Gurge sounds can be heard, and digital examination of the rectum shows a large empty ampulla. A number of X-ray findings may be present. Conservative treatments consist of detorsion by enemas or by passing a tube through a proctoscope beyond the obstruction carefully avoiding instrumental perforation. Surgical treatment consists of a laparotomy accompanied by insertion of tube into the rectum and detorsion. If gangrene is present bowel resection should be done, closing and inverting the distal stump, using the proximal for a temporary colostomy and later anastomosing the two segments. Exteriorization is not satisfactory. Sigmoidostomy and cecostomy are ineffectual.

J. DUFFY HANCOCK.

ANDERSON, L. Acute diverticulitis of the cecum. Surgery, 22: 479 (Sept.) 1947. Nine cases of acute diverticulitis of the cecum are reported. These cases were reviewed with 91 previously reported cases. The average age was rather young, 39.1 years. The cases were rather equally divided between males and females. The preoperative diagnosis in 84 per cent of the cases was some type of appendicitis. The commonest operative procedure was

simple excision or diverticulectomy. Right colectomy and cecectomy were done in a large number of cases because of inability to differentiate the inflammatory mass from malignancy which is more common in the cecum. X-ray is of little value in diagnosis since the use of barium enemas is contraindicated when the most probable diagnosis is acute appendicitis.

J. DUFFY HANCOCK.

#### LIVER AND GALL BLADDER

DAVISON, W. T. The post-cholecystectomy syndrome, incidence, etiology and treatment. *Am. J. Dig. Dis.*, 14: 290 (Sept.) 1947.

The author presents a general discussion and review of the post-cholecystectomy syndrome, defining it as "a recurrence of symptoms following removal of the gall bladder resembling or identical to those which persisted prior to operation". He believes that the chief cause of the post-cholecystectomy syndrome is dyskinesia of the sphincter mechanism, and discusses various forms of therapy including diet, antispasmodic drugs, and the "biliary flush regimen" suggested by Best.

The well substantiated comment is made that symptoms are particularly likely to occur when cholecystectomy is performed upon patients who do not have cholelithiasis or gross disease of the gall bladder wall. Figures are quoted to indicate that from 30 to 40 per cent of cholecystectomized patients, presumably those who did not have gall stones, complain of some or all of the symptoms they had prior to operation.

HENRY TUMEN.

MARTENSSON, K. Grave ascending cholangitis following cholangiography carried out through the cystic duct infected with *E. coli*. *Acta Chir. Scand.*, 94: 1 (June) 1946.

The author analyzed 491 cases of cholecystectomy, 303 of which had been subjected to cholangiography. Dogs and rabbits were subjected to intubation and injection of the hepatic ducts. He con-

cludes that cholangiography in the presence of infection by *E. coli* produces an ascending cholangitis in 100 per cent of animals and in 50 per cent of human beings. Primary common bile duct drainage may reduce the severity of this complication.

PHILIP LEVITSKY.

KELSALL, A. R., STEWART, A., AND WITTS, L. J. Subacute and chronic hepatitis. *Lancet*, 253: 195 (Aug.) 1947.

Hepatitis is divided clinically into 2 main groups: (1) cases with rapid onset of acute hepatitis which may progress to either rapid recovery, rapid death (acute yellow atrophy), a subacute stage with ultimate recovery, a subacute stage ending fatally, or chronic hepatitis; and (2) cases with insidious onset which may terminate fatally or progress to chronic hepatitis. The etiologic agent may be infection; chemical toxins such as arsenic, carbontetrachloride, trichlorethylene; or bromides. Some cases have been presumed to arise as a result of malnutrition, or an Rh incompatibility. Chronic alcoholism was not a significant factor in this series of cases. The diagnostic features are gastrointestinal disturbances, jaundice, fever, and a palpable tender liver. There may also be hemorrhagic manifestations, cutaneous spider naevi, ascites and even pleural effusion. Biochemical investigations may reveal impaired liver function as abnormal plasma bilirubin concentration, alkaline phosphatase, albumin-globulin ratio, and disturbed liver function tests. Radiologic examination, if it reveals esophageal varices, is of diagnostic significance.

PHILIP LEVITSKY.

LINDBERG, H. A. AND LEROY, G. V. Excretion of urobilinogen in the urine in infectious hepatitis. *Arch. Int. Med.*, 80: 175 (Aug.) 1947.

The usefulness of serial determinations of the two-hour excretion of urobilinogen in the urine, in the management of patients with infectious hepatitis, was studied, and this test was compared with other standard tests of liver function in a group of 120 patients in a hospital on Guadalcanal.

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The normal range for the two-hour period from 2-4 p.m. was found to be 0.6-0.8 Ehrlich unit. In the hepatic dysfunction unit. Often abnormal values did not appear until the icteric index had begun to decline from its maximum level. During convalescence there was a wide fluctuation in excretion until recovery, at which time normal values became constant. In most cases the urobilinogen excretion leveled off two to three weeks after the icterus index had returned to normal. Daily determinations appeared desirable to assure the absence of intermittent increases.

The bromsulfophthalein (5 mg. per kg.) dye retention, the cephalin-cholesterol flocculation, and the alkaline phosphatase tests were compared with the serial estimation of urobilinogenuria in an attempt to evaluate relative usefulness. The authors considered that the excretion of urobilinogen in the urine was the test least likely to give normal results while jaundice was present in acute infectious hepatitis, and the one most likely to give abnormal results after jaundice had subsided. They recommend that quantitative estimation of the urobilinogen in the urine be performed at least every other day during the convalescent period of a patient with infectious hepatitis.

EDGAR WAYBURN.

### ULCER

HARKINS, H. N., HOOKER, D. H., ALFORD, T. C., JR., CALLANDER, J., ELLIOTT, S. R., II, KEARNS, W., JR., MITCHENER, J., AND COOLEY, D. A. Symposium on vagotomy for peptic ulcer. I. Experimental observations. *Bull. Johns Hopkins Hosp.*, 81: 79 (Aug.) 1947.

This paper presents the results of experiments in the study of ulcer. The experiments included: (1) an attempt to produce histamine ulcers in the rat, (2) to produce aqueous benadryl solution in an attempt to prevent histamine-in-beeswax ulcers in the guinea-pig, (3) the use of benadryl-in-beeswax in an attempt to prevent the histamine-in-beeswax ulcers in the guinea-pig, (4) the use of vagotomy in attempt to prevent histamine-in-beeswax ulcers in the guinea-

pig, (5) the use of vagotomy in preventing pyloric-ligation induced ulcer, and (6) the influence of vagotomy on the development of jejunal ulcers in the Mann-Williamson dog.

It was observed that benadryl given either by mouth or subcutaneously in aqueous or beeswax-in-oil solution did not prevent histamine-provoked peptic ulcers in guinea-pigs. Vagotomy also did not prevent histamine-provoked ulcers, but did prevent the development within 24-hours of ligation-induced ulcers in rats and lengthened the life of these animals. Vagotomy decreased the acidity and volume of the accumulated gastric fluid following pyloric ligation in rats. Esophageal ligation, with or without vagotomy, reduced the incidence of pyloric-ligation-induced ulcers. Vagotomy performed on an average of 51 days after the Mann-Williamson operation in dogs decreased the incidence of peptic ulcer after the operation from the control level of 85 per cent to 11 per cent.

HENRY TUMEN.

JOHNS, T. N. P. AND GROSE, W. E. Symposium on vagotomy for peptic ulcer. II. Early surgical results in peptic ulcer cases. *Bull. Johns Hopkins Hosp.*, 81: 92 (Aug.) 1947.

This is a report of the early results in 43 vagotomized patients. None of these patients had been followed for more than 2 years and only two for more than 12 months. The report, therefore, cannot be considered as being more than preliminary. Of the 43 vagotomies, 3 were combined with splanchnectomy, 10 with the production of a new stoma, 14 with some form of resection, and in the remaining 16 cases no operation other than the vagotomy was performed.

As is true of many of the reports concerning vagotomy, many problems are demonstrated. One significant feature have been studied. One significant feature is the report of the performance of "prophylactic" vagotomy after the closure of a perforated ulcer. This was done in 10 cases, in 9 of these between 10 and 14 days after the closure of the perforation. Transthoracic vagotomy was done with the hope that heal-

ing of the ulcer would be facilitated and future difficulty prevented. In 37 of the cases which were suitable for statistical analysis, satisfactory results were obtained in 33 and unsatisfactory results in 4. These 4 unsatisfactory cases were all in the group in which vagotomy was performed without any other procedure. It must be noted that this is a high incidence of failure—4 out of 15 (27%) in the first year. Of these 4 patients, 2 have been relieved by subsequent operations on the stomach, and additional operations are being considered for the other 2. Three of these patients had marked gastroplegia. One patient who suffered recurrence of his ulcer had a complete vagotomy as determined by the insulin test.

Comment is made upon the apparent disparities between gastric secretory and motor loss in patients following vagotomy. Usually, these two gastric functions are diminished to comparable degrees after the operation but the relationship between them is by no means constant. Patients were observed who had complete loss of vagal secretory response with no abnormalities in the gastric motor function, as demonstrated by X-ray. Bizarre results may be the result of incomplete vagal section, inconsistencies of the insulin tests, and the possibility that it may not be necessary to cut all of the vagal fibers in order to effect apparent cure. One patient was observed in whom satisfactory results, at least for 12 months, were obtained with no impairment of the secretion or disturbance in motility. The most satisfactory result of the operation was the disappearance of ulcer pain. However, a postoperative motor paralysis of the stomach was frequently annoying and was observed in 67 per cent of the patients studied.

HENRY TUMEN.

PAULSON, M. AND GLADSDEN, E. S. Medical aspects of vagotomy for peptic ulcer. Including observations on the clinical value of the insulin test and on post-operative criteria for the completeness of bilateral vagus section. Bull. Johns Hopkins Hosp., 81: 107 (Aug.) 1947.

This is a further analysis of the same group of patients presented by Johns and Grose

(see previous abstract). Fourteen patients were studied in whom vagotomy was done either along with or following suturing of a perforated ulcer. In 10 of these vagotomy was done in conjunction with creation of a new stoma, and in 15 vagotomy was combined with subtotal gastric resection. These 39 cases were followed for periods up to 1 year. Striking relief was obtained immediately after operation. In 3 individuals there was pain recurrence within a few months. In 1, subtotal resection was done because of previous gastric resection. In other patients, the recurrence of bleeding indicated the probable reactivation of the ulcer. In those individuals who had vagotomy without any other operation on the stomach except suturing of the perforated ulcer, post-operative fullness was noted necessitating further surgical intervention in 2 cases. The appetite improved and there was gain in weight in most instances. Relief of preoperative constipation was noted in the majority of patients; diarrhea was observed occasionally.

Gastroscopic examination of the stomach following vagotomy showed no change in the gastric mucosal pattern. The stomach was observed to be less active, with lessened peristaltic movement. The pyloric sphincter remained open. In those patients in whom vagotomy was combined with subtotal gastrectomy, the edema, thickening and hypertrophy of the mucosa was similar to that observed in patients who had had resection without vagotomy.

In 2 patients, elevation of serum amylase occurred after vagotomy, but in 5 the amylase was normal both before and after operation, and no conclusion of the effect of vagotomy on pancreatic function seems justified. The insulin test is discussed and difficulties in interpretation in patients who have subtotal gastrectomies or gastroenterostomies were commented upon. The insulin test was found to be more satisfactory in patients with only vagotomy. A question is raised concerning the validity of the insulin test as a measure of the success of vagotomy, particularly since it is stated that there are no determinable subjective or objective differences within the first year after vagotomy in those patients with

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positive and negative responses to this test. Complete vagal section may not be obtainable in all instances and may not be necessary. It remains to be proved, according to the authors, that a single positive insulin test in itself indicates inadequate, and therefore unsatisfactory, vagal section from a clinical standpoint. The complete relief given by vagotomy may not be an unmixed blessing and diagnostic problems may arise because of loss of pain sensation both in patients who develop recurrent ulcers and those who develop gastritis. The indications for vagotomy are discussed and it is stressed that vagotomy may reduce the incidence of recurrences in patients who have had ulcer perforation.

HENRY TUMEN.

MOORE, F. D. Resection of the vagus nerves for ulcer: An interim evaluation. *Arch. Surg.*, 55: 164 (Aug.) 1947.

The operative technique, postoperative management, and hospital morbidity and mortality in a series of 74 patients with ulcer treated by resection of the vagus nerves, are reported. The thoracic approach was used in 97 per cent of the cases. Gastroenterostomy was primary in 2 cases and necessary postoperatively in 2 others. Good results were obtained 2 to 30 months following operation, in 87 per cent of the cases. Five patients have had frankly poor results, and 5 others had side effects detracting materially from their result.

C. WILMER WIRTS, JR.

WARREN, R. Experiences with vagectomy for peptic ulcer. *Surgery*, 22: 246 (Aug.) 1947.

Vagectomy has opened a new era in the surgery of peptic ulcer and promises to decrease greatly the disability caused by that disease. It is indicated especially in the young group uncontrolled by medical therapy, showing a high degree of stress sensitivity, having highly acid gastric secretion with copious night secretion, and presenting no cicatricial pyloric obstruction. Another favorable group includes cases with stomal ulcers. A less favorable group comprise the intractable middle-aged patients without copious night secretion, or with

complicating factors like chronic alcoholism, Buerger's disease, and psychoneurosis. Contraindications include recent massive hemorrhage in patients over 45, or active bleeding at the time of surgery, at any age; diagnostic uncertainties, mechanically poor, ill-advised previous surgery; and pyloric obstruction. The transthoracic operative approach is preferred. The lower 5 cm. of the esophagus offers the most satisfactory site for identification of the vagus fibers. In a series of 15 cases all but 3 of 14 recently checked are clinically well. Two had mild symptoms of retention with vomiting once or twice a week, and one developed a flare-up of his duodenal ulcer and two additional gastric ulcers requiring gastric resection.

J. DUFFY HANCOCK.

HARKINS, H. N. AND HOOKER, D. H. Vagotomy for peptic ulcer. Experimental and clinical studies. *Surgery*, 22: 239 (Aug.) 1947.

Vagotomy was performed in two laboratory experiments. In one, Mann-Williamson dogs were used with a tremendous reduction in incidence of jejunal ulcers when vagotomy was done. In the second series of experiments, the same results were observed in rats where ulcers induced by pyloric ligation were studied. In clinical cases the symptomatic results of the operation were:—marked relief of pain, relative diarrhea, and delayed gastric emptying time. The pain relief more than compensated for the disagreeable effects, since the latter showed a tendency to subside in the late postoperative period. There were four failures in 36 cases; two of the four appeared to be due to incomplete operation.

J. DUFFY HANCOCK.

SMALL, J. T. Denervation of the stomach. Historical review. *Arch. Surg.*, 55: 189 (Aug.) 1947.

A review of the literature shows that the results of experimental gastric denervation have been recorded for at least 133 years and employed for clinical relief of pain, hypersecretion, and hypermotility for about 50 years. It was generally agreed that gastric denervation is efficacious in the treatment of

gastrojejunal ulceration, but there is no general agreement concerning the direct loss of sensation of visceral pain; those effects have been ascribed to reduced motility of the stomach and also to interruption of the sympathetic afferent nerves. Insufficient time has elapsed since the current intensive use of vagotomy was initiated, to indicate the permanency of the favorable and unfavorable results of this operation, and its proper place in the therapy of peptic ulcer.

C. WILMER WIRTS, JR.

OLIVER, J. V. Effect of vagotomy on development of the Mann-Williamson ulcer in the dog. *Arch. Surg.*, 55: 180 (Aug.) 1947.

This investigation was conducted to determine: (1) the effect of preliminary vagotomy on the development of jejunal ulcer in dogs on which the Mann-Williamson operation was done, and (2) the effect on the formation of ulcer when the vagotomy was performed after the Mann-Williamson operation. A third group in which the Mann-Williamson operation only was performed was used for control. Of 9 dogs in the control series, 6 (67%) developed ulcer. The other 3 dogs in this group died so soon after operation that there may have been no opportunity for the formation of ulcer. Of the 5 dogs in which vagotomy followed the Mann-Williamson operation, all (100%) developed ulcer, and of the 7 in which the Mann-Williamson operation followed the vagotomy 5 (71%) developed ulcer. The author concludes that although vagotomy did not prevent ulcer in the above experiments, no correlation can be drawn with clinical results because the pathogenesis of the experimental and human peptic ulcer is different.

C. WILMER WIRTS, JR.

GRIMSON, K. S., BAYLIN, G. J., TAYLOR, H. M., HESSER, F. H., AND RUNDLES, R. W. Clinical evaluation of complications observed after transthoracic vagotomy. *Arch. Surg.*, 55: 175 (Aug.) 1947.

Fifty-seven patients with refractory or frequently recurring peptic ulcer were treated by transthoracic vagotomy or transthoracic vagotomy and gastroenterostomy. Exact statistics of complications are

presented. Vomiting, hematemesis, or mild pain like that of ulcer, occurred occasionally in the group with vagotomy alone and rarely, if at all, in the group with vagotomy and gastroenterostomy. In the former group, symptoms of fullness after eating, foul eructations, and swelling of the abdomen were frequent during the first 3 months but thereafter occurred about equally in the two groups. Mild colicky abdominal cramps occurred about equally in the two groups. There was a greater tendency toward looseness of the stools in the group with vagotomy alone, while in those with gastroenterostomy there was a higher incidence of serious diarrhea. Secondary gastroenterostomy was necessary in 5 of 41 patients originally treated by vagotomy alone, and 2 patients with vagotomy alone are at present having serious difficulty with gastric retention. The authors conclude that transthoracic vagotomy should not be used as a standard treatment of duodenal or gastric ulcer, but it may be of value when combined with gastroenterostomy or when employed for stomal ulcer.

C. WILMER WIRTS, JR.

SALTZSTEIN, H. C., SANDWEISS, D. J., HAMMER, J. M., HILL, E. J., AND VANDENBERG, H. J. Effect of vagotomy on Mann-Williamson ulcers in dogs. *Arch. Surg.*, 55: 130 (Aug.) 1947.

The postoperative survival time of dogs, on which the Mann-Williamson operation and also transthoracic vagotomy were performed, was much shorter than that of the control animals. In 6 or 8 dogs on which both operations were done and which lived one month, ulcer developed. Gastric dilatation was present in 75 per cent of the vagotomized dogs, most frequently in those of short survival. Jejunitis of varying severity was present in 60 per cent of the vagotomized dogs.

C. WILMER WIRTS, JR.

SALTZSTEIN, H. C., SANDWEISS, D. J., HAMMER, J. M., HILL, E. J., AND VANDENBERG, H. J. Effect of enterogastrone on Mann-Williamson ulcers in dogs. *Arch. Surg.*, 55: 125 (Aug.) 1947.

The effect of orally administered entero-

## ABSTRACTS OF CURRENT LITERATURE

gastrone, in a series of 15 dogs on which the Mann-Williamson operation had been done, was studied. Some beneficial therapeutic effect of the enterogastrone was demonstrated on the basis of a prolonged survival time of the treated series and the failure of 3 dogs (23%) to develop ulcer.

C. WILMER WIRTS, JR.

HARPER, P. V. AND DRAGSTEDT, L. R.  
Section of the vagus nerves to the stomach in the treatment of benign gastric ulcer. Arch. Surg., 55: 141 (Aug.) 1947.

During the past 4 years section of the vagus nerves to the stomach as a method of treatment has been carried out in 250 patients with various types of peptic ulcer. A mortality rate of 0.4 per cent is reported. Clinical results have been highly satisfactory. Eighteen patients were observed in whom section of the vagus nerves was probably incomplete. In this group, 6 patients complained of recurrent or persistent symptoms of ulcer and in 2, an undamaged vagus fiber was found at a second operation. Division of this nerve was followed by complete relief. The transabdominal approach was employed in the majority of the patients and the operation was combined with gastroenterostomy in 71 patients. In 5 cases, cicatrical obstruction at the pylorus required a subsequent gastroenterostomy.

Eight cases with gastric ulcer are reported in some detail. All the ulcers that were unquestionably benign healed promptly after total section of the vagus nerve. If the ulcer is in the antrum, resection is preferable, but if it is located high on the lesser curvature necessitating total gastrectomy for adequate removal, section of the vagus may be employed to advantage.

C. WILMER WIRTS, JR.

WALTERS, W., NEIBLING, H. A., BRADLEY, W. F., SMALL, J. T., AND WILSON, J. W.  
Gastric neurectomy. Arch. Surg., 55: 151  
(Aug.) 1947.

A total of 83 patients with duodenal, gastrojejunal, or gastric ulcer were subjected to gastric neurectomy alone, with gastroenterostomy or with excision of the ulcer. In general the results are inconstant,

variable, and in most cases unpredictable. Reduction in gastric acidity, although it has occurred in most cases, is inconstant in others. Disturbances of motility of the stomach and small intestine are frequent after operation. The relief of pain obtained may be the release of gastrospasm and a reduction in gastric acidity as a result of the interruption of the cephalic stimulation. The expense of this relief of pain is dilatation of the stomach with frequent troublesome retention of gastric secretion and in some cases remnants of food. Three hospital deaths occurred, two were directly attributable to cardiovascular accidents, whereas one patient died of unsuspected perforated duodenal ulcer with a subdiaphragmatic abscess.

It is concluded that the greatest field of usefulness for this operation seems to be in the treatment of ulcers after partial gastrectomy and in certain cases of nonobstructive duodenal ulcers in which the cephalic phase of gastric secretion is marked and pain is intractable.

C. WILMER WIRTS, JR.

STEIN, I. F., GROSSMAN, M. I., AND IVY, A. C.  
Experimental production of ulcers in closed gastric pouches in dogs. Surgery, 22: 522 (Sept.) 1947.

Three groups of dogs were operated upon with the production of a Heidenhain gastric pouch in each animal. In one group there was primary closure of the pouch, in another group secondary closure of the pouch was accomplished, and in the third group primary closure was used but the pouch was subjected to daily aspiration. In the majority of cases in each group acute ulcers with perforation developed in closed Heidenhain gastric pouches. Intraluminal pressure apparently enhanced the ulcerogenic action of acid pepsin.

J. DUFFY HANCOCK.

## SURGERY

HOERR, S. O. Factors in the reduction of mortality in acute appendicitis. Surgery, 22: 402 (Aug.) 1947.

A series of 382 patients operated upon for acute appendicitis with only one death prompted an analysis to determine the

cause for such favorable results. Penicillin played no part since it was available for only a few patients in this series. The favorably regarded McBurney incision was used in some of the cases. Some further reduction in the use of peritoneal drainage had been practiced but did not appear to be much of a factor. The increase in the use of blood and plasma was not significant. On the other hand the significant increase in the use of gastric suction seemed to play only a minor part since only 10 per cent of former deaths were due to obstruction. The principal factor was the systemic use of the sulfonamides (recently sulfadiazine exclusively) both preoperatively and postoperatively. This is easily understood when it is realized that formerly 70 per cent of the deaths were due to intra-abdominal sepsis.

J. DUFFY HANCOCK.

SWENSON, O. End-to-end anastomosis of the esophagus for esophageal atresia.

*Surgery*, 22: 324 (Aug.) 1947.

In 14 out of 20 infants studied, a primary anastomosis of the esophagus was done with a mortality of 6.6 per cent. The pre-operative care was accomplished in less than 48 hours. It consisted of gentle constant suction of the blind esophageal pouch, oxygen therapy, parental fluids, sulfadiazine and penicillin, and blood or plasma. The anesthetic of choice was cyclopropane with preliminary atropine, but no morphine. Blood was given during operation. The retroperitoneal approach was used and the best exposure obtained by resecting 1.5 cm. of the third, fourth, fifth, and sixth ribs. The mediastinum is entered by freeing the pleura from the thoracic cage and ligating and dividing the azygos vein. Maximum length of the lower esophageal segment is obtained by dividing the fistula close to the trachea. Because of its tougher structure the upper pouch can be pulled down by traction and dissection. It should be anchored by traction sutures to the perivertebral fascia. The anastomosis is accomplished by making a posterior muscular layer, a circular mucosal layer, and an anterior muscular layer using 5-0 silk on a half-circleatraumatic needle. A drain to the anastomosis site is brought out poster-

iorly. Postoperatively no catheter is used, and nothing given by mouth until the 10th day when water is begun in one-half ounce measures every 2 hours. The formula is added as tolerated. In this interim, feeding is accomplished through a Stamm gastrostomy performed under local anesthesia on the day following the primary anastomosis. Edema must be controlled to avoid tension on the suture line. While the anastomotic stoma was small, dilatation was required in only one case.

J. DUFFY HANCOCK.

BLOOM, J. Plasma clot graft of peritoneum for perforations of stomach. *Surg. Gyn. Obs.*, 85: 155 (Aug.) 1947.

A new experimental method of plasma clot graft of the peritoneum for perforations of the stomach is presented. The graft tides the patient over the acute period of perforation and thus enables the peritoneum more easily to combat infection due to leakage. It also serves as a temporary seal for the leak.

Nine dogs were used in this experiment. Perforations were produced with cautery through the stomach wall in the prepyloric or in the duodenal area. Four dogs survived one month or longer after closure of the perforation by the use of an artificial plug and fascial peritoneal graft application by the plasma clot technique. Death of the other five dogs was attributed to some defect in the graft technique.

FRANCIS D. MURPHY.

BRUNSCHWIG, A. One stage pancreateoduodenectomy. *Surg. Gyn. Obs.*, 85: 161 (Aug.) 1947.

The purpose of this paper is to present the somewhat infrequent incidence of pancreateoduodenectomy, the recognized procedure of dealing with cancer requiring excision of the lower stomach, the entire duodenum, and the head of the pancreas en masse. Seven cases of pancreateoduodenectomy are presented with a report of no surgical mortality. Survival is dependent on earlier diagnosis of lesions necessitating the operation.

FRANCIS D. MURPHY.

## ABSTRACTS OF CURRENT LITERATURE

KATE, J. T. A simple and aseptic method of ileocolostomy. *Surg. Gyn. Obs.*, 85: 217 (Aug.) 1947.  
Because serious infection may ensue in shortcircuiting a proximal and a distal loop of intestine by lateral anastomosis the author presents a simple and aseptic method of ileocolostomy. The advantage of this method is that an open communication is established immediately between the loops, thus eliminating the use of any specially constructed instrument.

FRANCIS D. MURPHY.

## PATHOLOGY

MEISSNER, W. A. Distribution of parietal cells in gastric disease. *Arch. Path.*, 44: 261 (Sept.) 1947.

A study of the distribution of the parietal cells in gastric disease—cancer, gastric and duodenal ulcer—was made on 200 specimens of stomachs removed at operation. Eighty-one per cent were resected for duodenal ulcer, 80 per cent for gastric carcinoma, and 39 per cent for gastric ulcer. Total gastrectomy was performed in too few instances to permit inclusion in this series of a study of the cells in the cardia.

The stomach was divided, for the purpose of comparative study into four zones: the fundus, the body, the pyloric antrum, and the pyloric canal. It was found, in general, that the number of parietal cells diminishes, as the pylorus is approached and is somewhat less along the lesser curvature than in the lateral walls and greater curvature. There was found a greater diminution of the cells in the body and fundus of the stomach in cancer than in ulcer, especially duodenal ulcer, but there was variation in these findings. In cancer, in which complete anacidity existed, there was often an abundance of parietal cells. In no instance was there complete absence of such cells. As regards the supposition that the diminution or absence of acid secretion in the stomach in the presence of gastric cancer is due to an associated gastritis no evidence was found to support this hypothesis. There were also no qualitative changes in individual parietal cells which could be correlated with ulcer or with cancer.

N. W. JONES.

## PHYSIOLOGY: MOTILITY

ANNEGERS, J. H. AND IVY, A. C. The effect of dietary fat upon gastric evacuation in normal subjects. *Am. J. Physiol.*, 150: 461 (Sept.) 1947.

Thirty normal subjects were given 1500 calorie test-meals of constant weight and volume, and containing 53, 77, and 120 grams total fat. Of this, 25, 50, and 80 grams, respectively, was lard or hydrogenated vegetable oil (Crisco). Four hours after the test meal the stomach was outlined with a small amount of barium sulphate suspension and an X-ray film was immediately made. Changes in the 4-hour volume of the stomach were detected by measuring the area of the projected gastric shadow. Delayed gastric evacuation attributable to the fat content of the test meal was statistically significant. Twenty-five subjects showed a delay at four hours when the fat content by wet weight was increased from 6 to 8 per cent and 27 subjects showed delayed gastric evacuation when the fat was increased from 8 to 14 per cent. No significant differences were found between lard and hydrogenated vegetable oil in their effect on gastric emptying. No gastrointestinal symptoms followed any of the test meals. The gastric inhibition which occurred when the fat content of the meal was increased was a consistent characteristic for any given individual.

ARTHUR E. MEYER.

## MISCELLANEOUS

COOPER, W. A. A method of statistical analysis. *Surgery*, 22: 367 (Aug.) 1947. Various statistical methods are described for evaluating the results of ulcer surgery. While the statements given are accurate in most, the implications are often inaccurate. Some methods are rather cumbersome and others require discarding of valuable experience. A new plan is suggested which is graphic and easily adaptable to standard methods. This method is most important, since it makes it possible to report every case in a series without selection of material within the series. Several illustrative charts are presented.

J. DUFFY HANCOCK.

GRIMSON, K. S., HESSER, F. H. AND KITCHIN, W. W. Early clinical results of transabdominal celiac and superior mesenteric ganglionectomy, vagotomy, or transthoracic splanchnicectomy in patients with chronic abdominal visceral pain. *Surgery*, 22: 230 (Aug.) 1947.

A preliminary study of the effects of interrupting visceral sensory pathways is reported. It was found that abdominal visceral pain is transmitted by sensory afferent nerves through the splanchnics and not through the vagi. Chordotomy seems preferable to splanchnicectomy for the relief of gastric crises of tabes dorsalis. Vagotomy appears to be contraindicated. Postoperative biliary dyskinesia shows relief of pain following right celiac and partial left celiac and superior mesenteric ganglionectomy. Ganglionectomy without vagotomy seems a better procedure than with vagotomy for severe unexplained abdominal pain, since it avoids symptoms of gastric retention.

J. DUFFY HANCOCK.

CULVER, G. J. AND CLARK, S. B. The radiographic diagnosis of perforations of the upper gastrointestinal tract into the mediastinum and pleural cavity. *Surgery*, 22: 458 (Sept.) 1947.

A sudden increase in pressure, such as that resulting from a blow to the abdomen or from vomiting and retching, is a contributing factor in the etiology of spontaneous esophageal perforation. The symptoms are suggestive of coronary thrombosis, pulmonary embolism, dissecting aneurysm of aorta, spontaneous pneumothorax, acute pancreatitis, gastric perforation or mesenteric thrombosis. X-ray findings include mediastinal widening and emphysema, and most significantly a hydropneumothorax. Aspiration of gastric contents from the pleural cavity is pathognomonic when it is taken in consideration with the history and the likelihood that the hydropneumothorax is recent. Four cases are reported.

J. DUFFY HANCOCK.

HUNTER, W. C. AND RICHARDSON, H. L. Cytologic recognition of cancer in exfoliated material from various sources. *Surg. Gyn. Obs.*, 85: 275 (Sept.) 1947.

A modified method of obtaining vaginal fluid to diagnose cancer is presented by the authors. This method has proved most gratifying, since by its use, cells of all kinds are well preserved and are concentrated. This obviates the necessity of long search over wide areas. In the hands of an experienced cytologist, the groups of cells are not torn apart as is very likely to happen with smearing. The Papanicolaou stain can be employed easily in this procedure.

This method has proved effective in diagnosing carcinoma of the bladder, rectum, stomach, and bronchus, as well as carcinoma of the uterus.

FRANCIS D. MURPHY.

KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., AND SALTZSTEIN, H. C. Alterations in urogastrone excretion produced by extirpation of various endocrine glands. *Am. J. Physiol.*, 150: 373 (Sept.) 1947.

Extracts prepared from the urine of normal dogs (urogastrone) inhibit gastric secretion and decrease the acidity of gastric juice. Urogastrone made from thyroidectomized plus oophorectomized dogs exerts nearly the same inhibitory influence as urogastrone procured from normal animals. However, when the ovaries alone are removed, the depressing effect of the extract is less marked than that of normal urogastrone. Hypophysectomized dogs do not produce urogastrone in adequate amounts to diminish gastric secretion. On the contrary, urine extracts of such animals increase the quantity and the acidity of the gastric juice secreted after histamine injection. The conclusion is drawn that the pituitary gland plays a role in the formation or excretion of urogastrone.

ARTHUR E. MEYER

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- Beck, A. C.: *Obstetrical Practice*, Ed. 3, Baltimore, Williams & Wilkins Company., 1942, p. 570.
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  - \*DeLee, J. B., and Greenhill, J. P.: *Principles and Practice of Obstetrics*, Ed. 9, Philadelphia, W. B. Saunders Company., 1947, p. 83.
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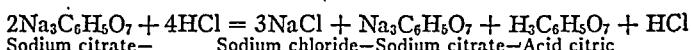
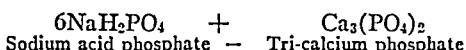
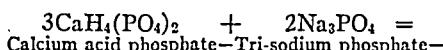
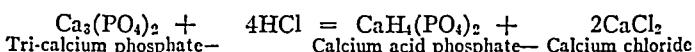
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# ANNOUNCEMENT

## *Information Regarding Post-Graduate Instruction in Gastroenterology*

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

Name	Place	Name	Place
Aaron, A. H.	Buffalo, N. Y.	Miller, T. Grier	Univ. of Pennsylvania
Atkinson, Arthur	Passavant Hospital, Chicago	Moser, Rollin H.	Indianapolis
Balfour, Donald	Mayo Clinic	Neches, H.	Michael Reese Hospital, Chicago
Benedict, Edward B.	Harvard Medical School	Palmer, Walter L.	University of Chicago
Bockus, Henry L.	Univ. of Pennsylvania	Patterson, Cecil O.	Dallas, Texas
Carey, James B.	The Nicotlet Clinic, Minneapolis	Perry, Thomas M.	Georgetown Univ., Wash., D. C.
Crohn, Burrill B.	New York	Pollard, H. M.	Ann Arbor, Mich.
Garbat, A. L.	Lenox Hill Hospital, N. Y.	Rafsky, H. A.	Lenox Hill Hospital, N. Y.
Gray, Irving	Brooklyn	Rehfuss, Martin E.	Jefferson Med. College
Gorham, L. W.	Union University, Albany, N. Y.	Renshaw, R. J. F.	Cleveland Clinic
Hardt, Leo L.	Chicago	Ruffin, Julian M.	Duke University
Hollander, Franklin	Mount Sinai Hospital, New York	Silverman, Daniel N.	New Orleans, La.
Ivy, A. C.	University of Illinois	Sydenstricker, V. P.	University of Georgia
Laing, Grant H.	Chicago	Twiss, J. R.	Post Grad. Med. School, New York
Layne, John A.	Great Falls Clinic, Montana	Watson, C. J.	University of Minnesota
Mateer, John G.	Henry	Wilkinson, S. Allen	Lahey Clinic, Boston
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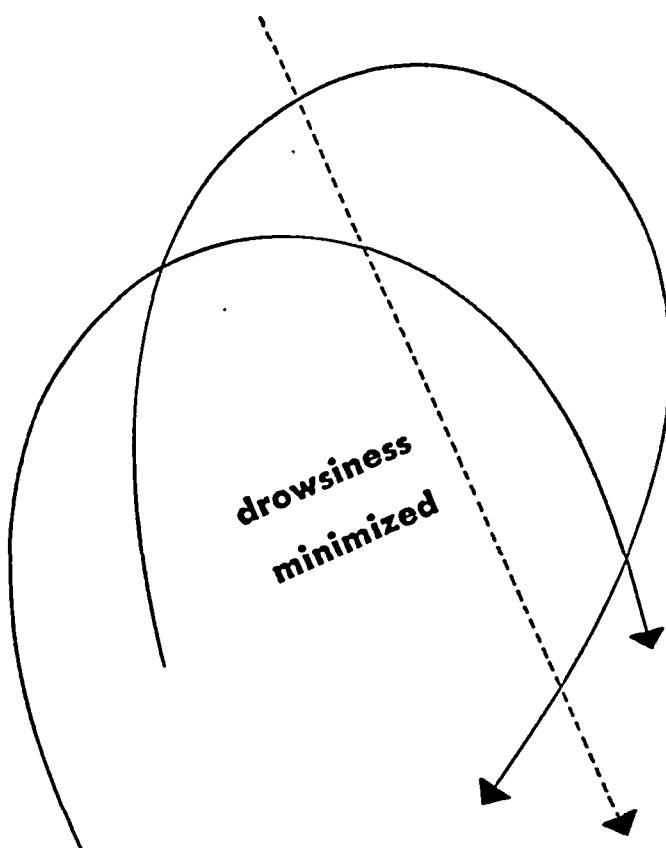
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**GASTROENTEROLOGY***Official Journal of the American Gastroenterological Association*WALTER C. ALVAREZ, *Editor*A. C. IVY, *Assistant Editor*

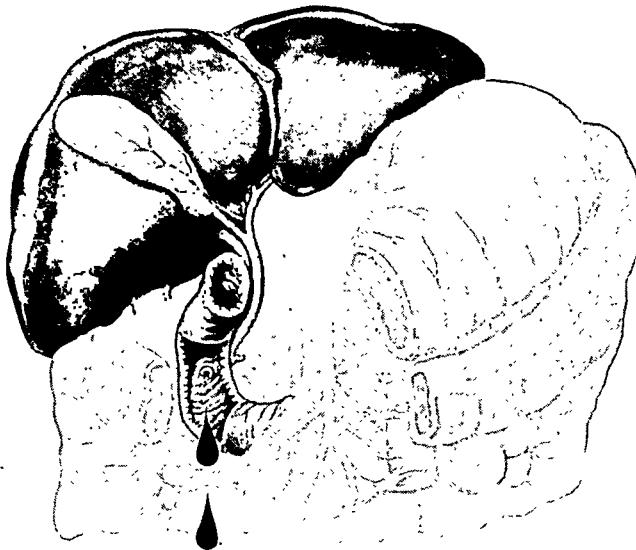
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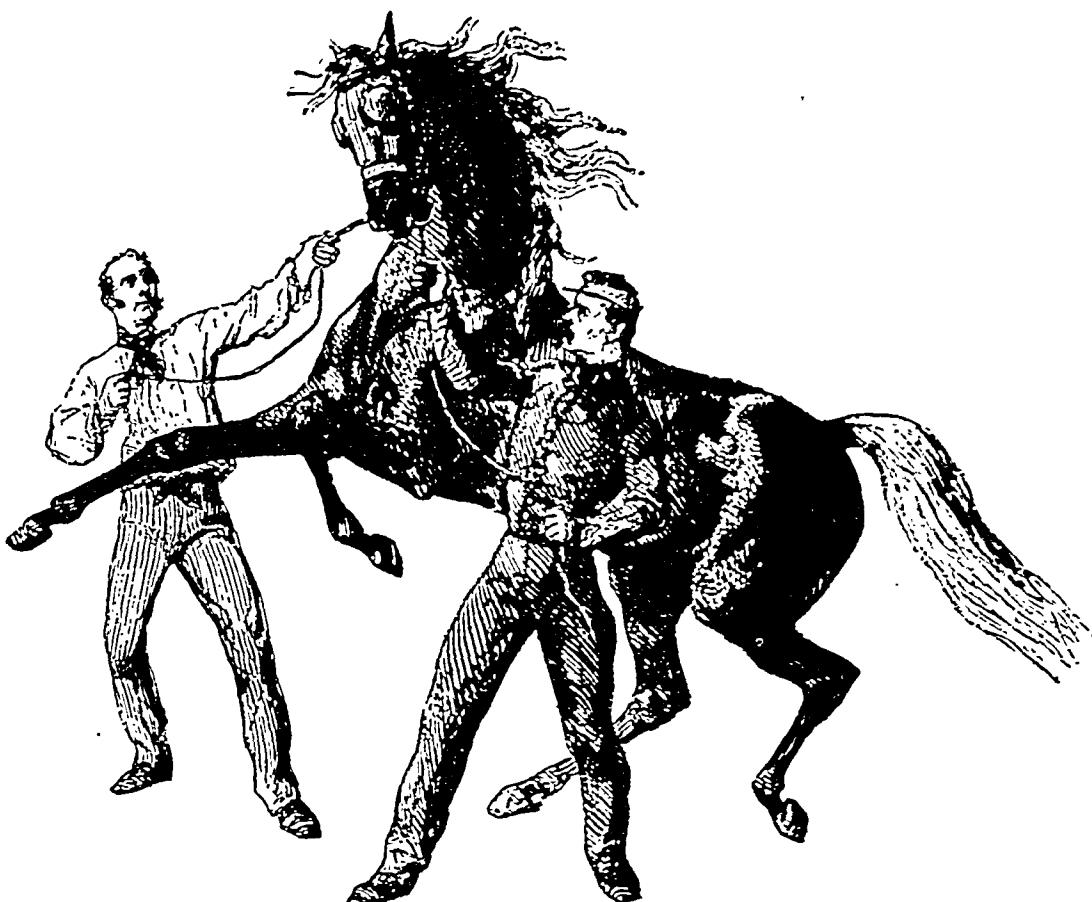
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\*Albrecht, F. K.: Modern Management in Clinical Medicine, Baltimore, The Williams and Wilkins Co., 1946, p. 170.

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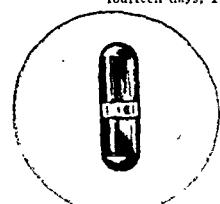
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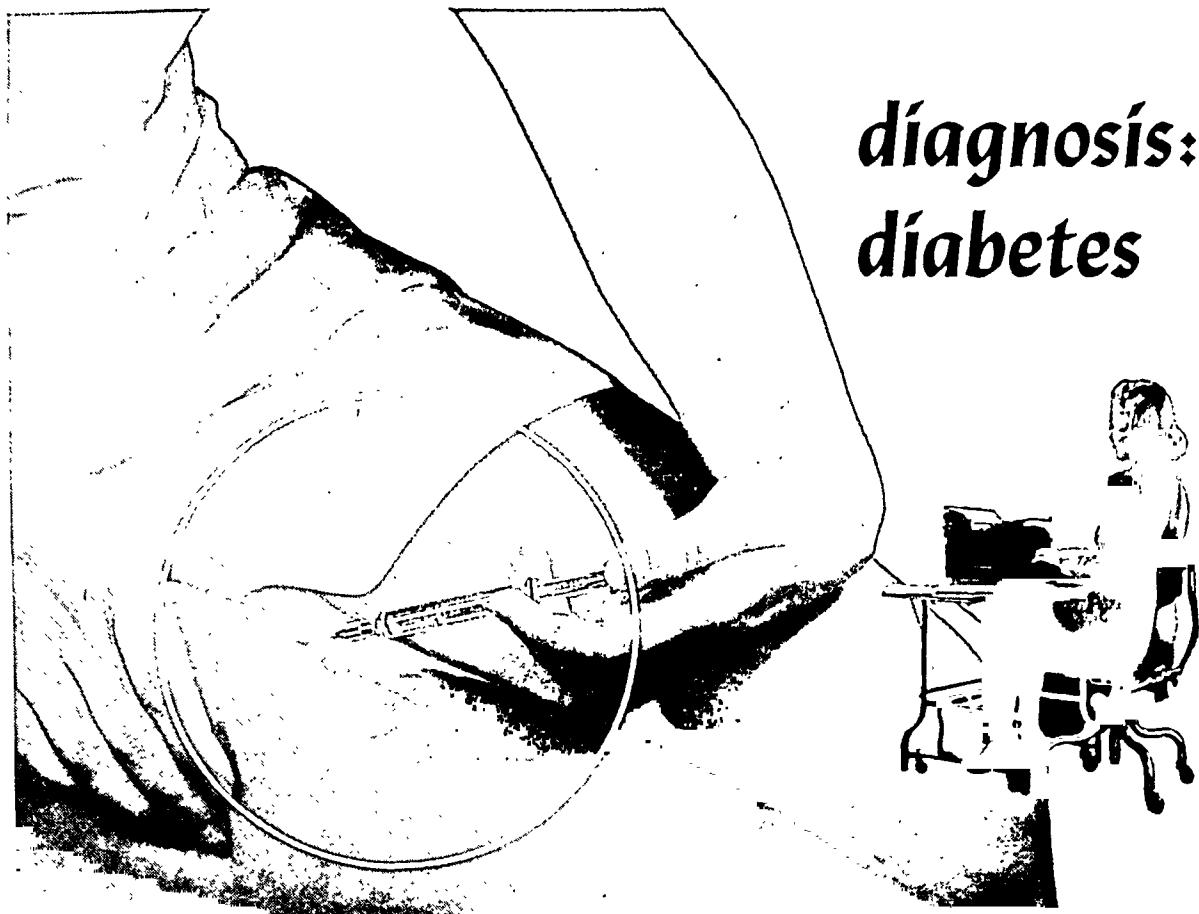
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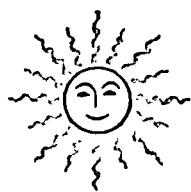
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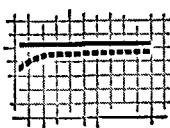
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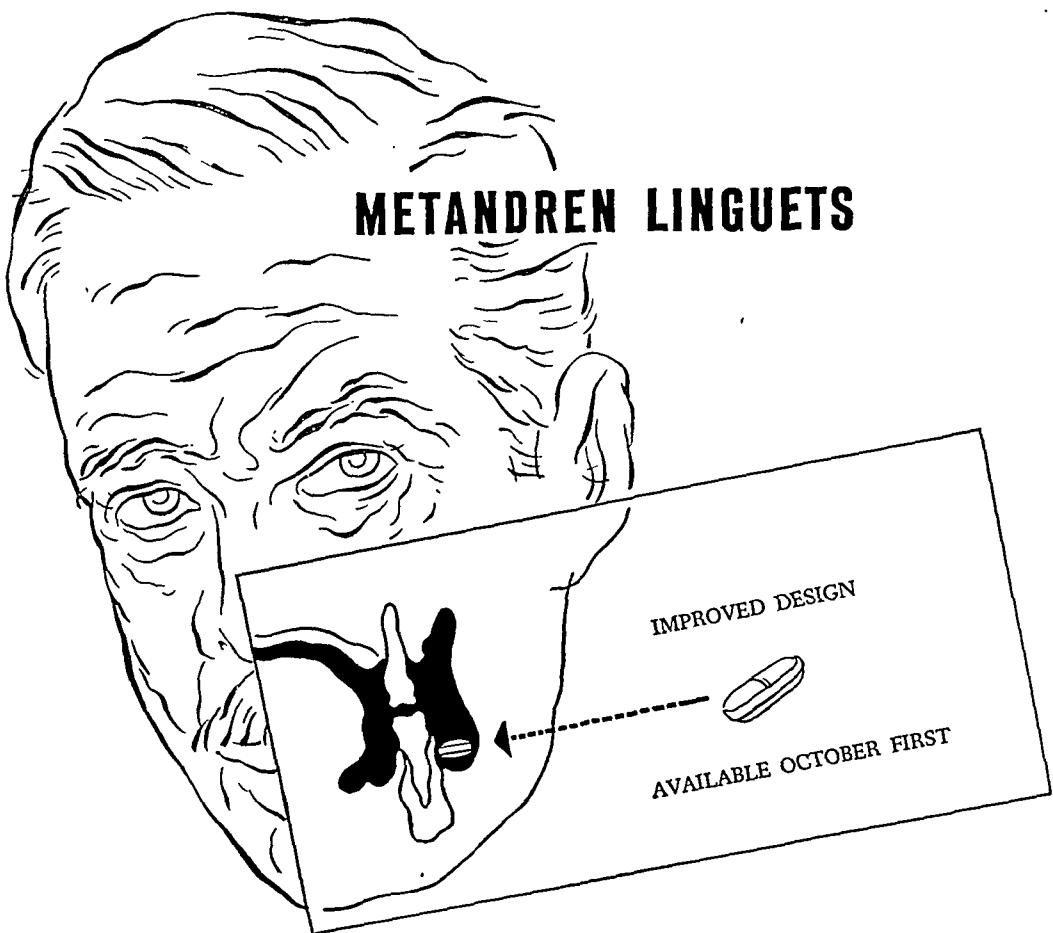


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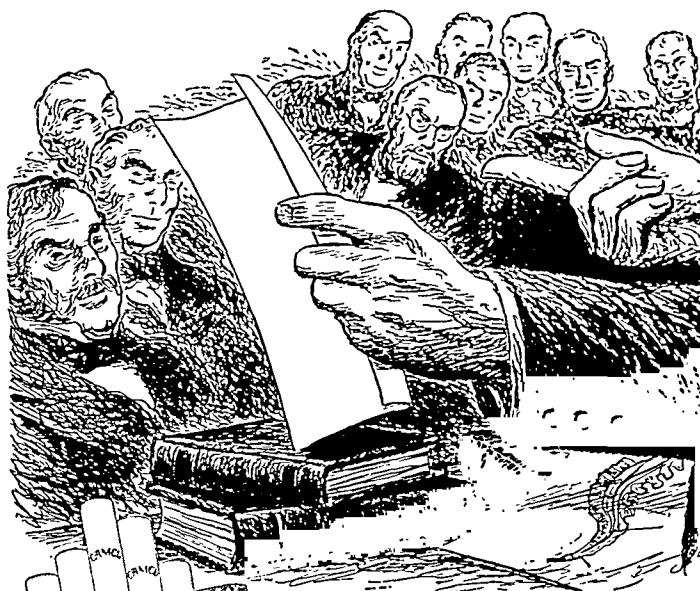
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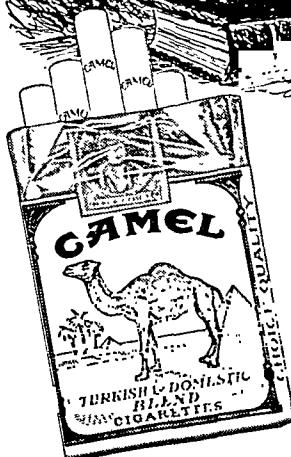
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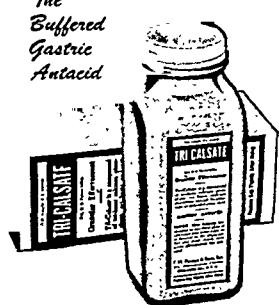
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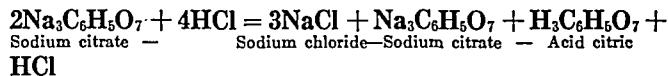
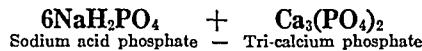
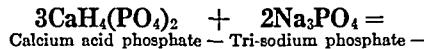
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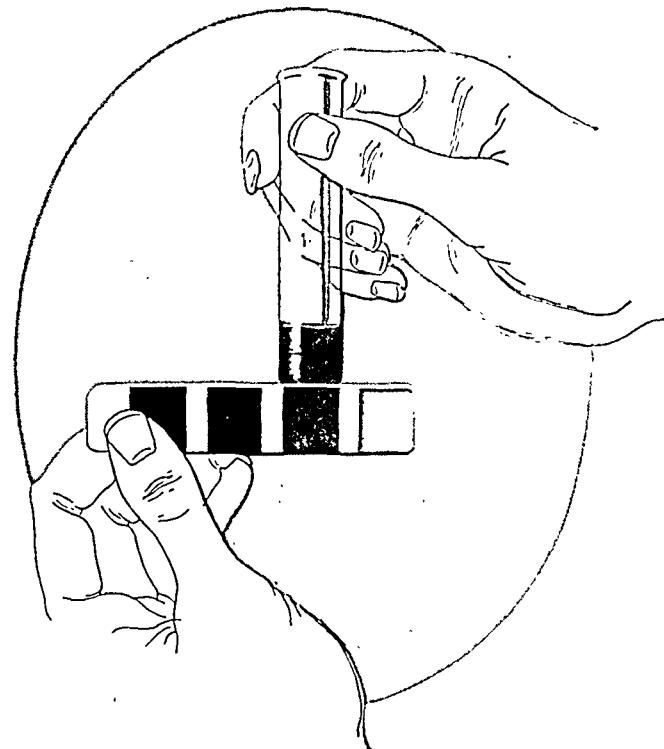
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# GASTROENTEROLOGY

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## AN OPERATING GASTROSCOPE\*

EDWARD B. BENEDICT, M.D.

*From the Massachusetts General Hospital, Boston*

The importance of biopsy in bronchoscopy, esophagoscopy, thoracoscopy, peritoneoscopy, and cystoscopy can hardly be overemphasized. Although the flexible gastroscope has made notable contributions in the diagnosis of gastric disease, biopsy has heretofore been impossible, and mistakes have been made in the differential diagnosis of benign and malignant gastric ulcer, gastritis and

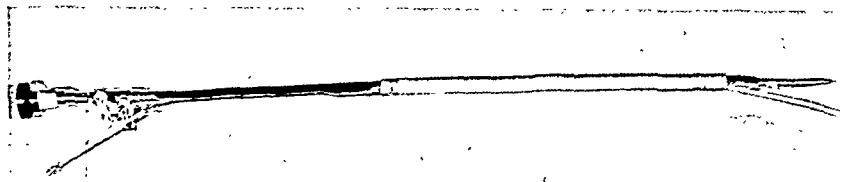


FIG. 1

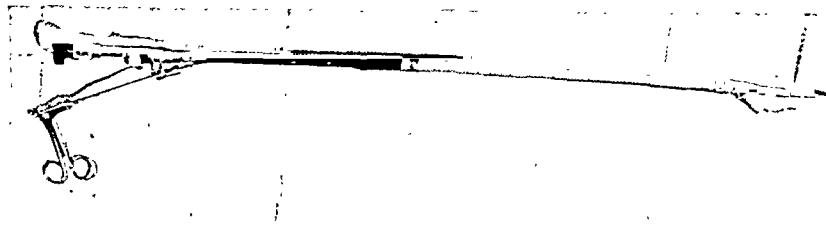


FIG. 2

carcinoma, lymphoma, sarcoma, etc. I believe many of these errors in diagnosis can be avoided by the judicious use of the new gastroscopic biopsy forceps.

Ever since Schindler<sup>1</sup> invented the flexible gastroscope in 1932 and I<sup>2</sup> began using it in this country in 1933, I have been hoping for and working toward a satisfactory method of aspirating secretions and obtaining a biopsy. With

\* Presented at the Annual Meeting of the American Gastroenterological Association and at the Annual Meeting of the American Gastroscopic Society, Atlantic City, April 30 and May 2, 1948.

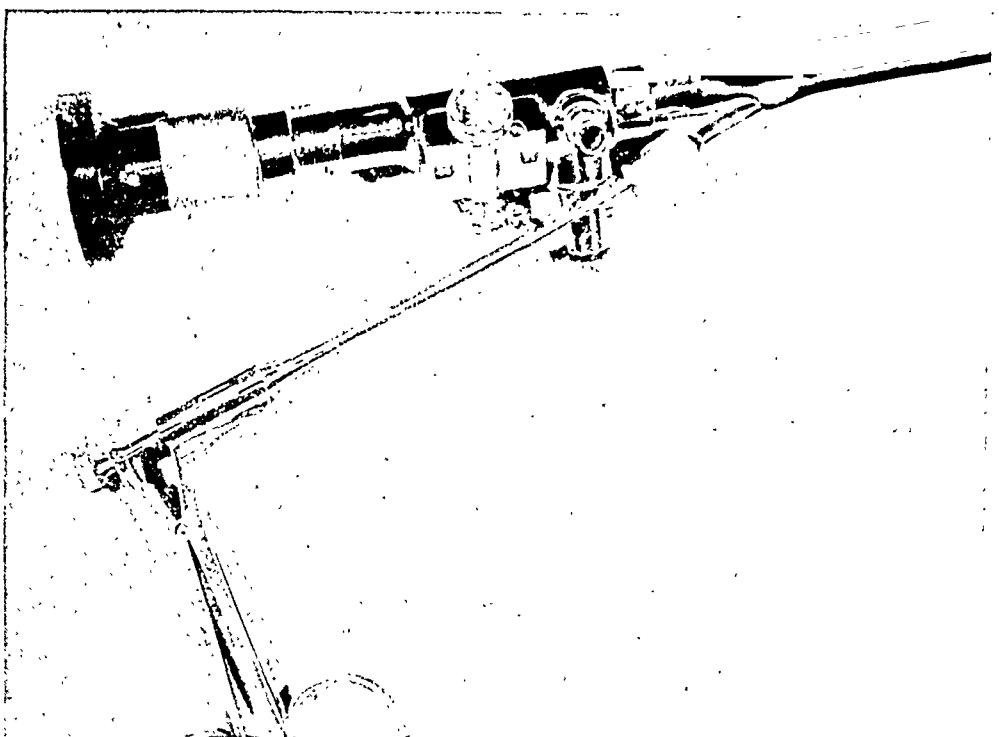


FIG. 3

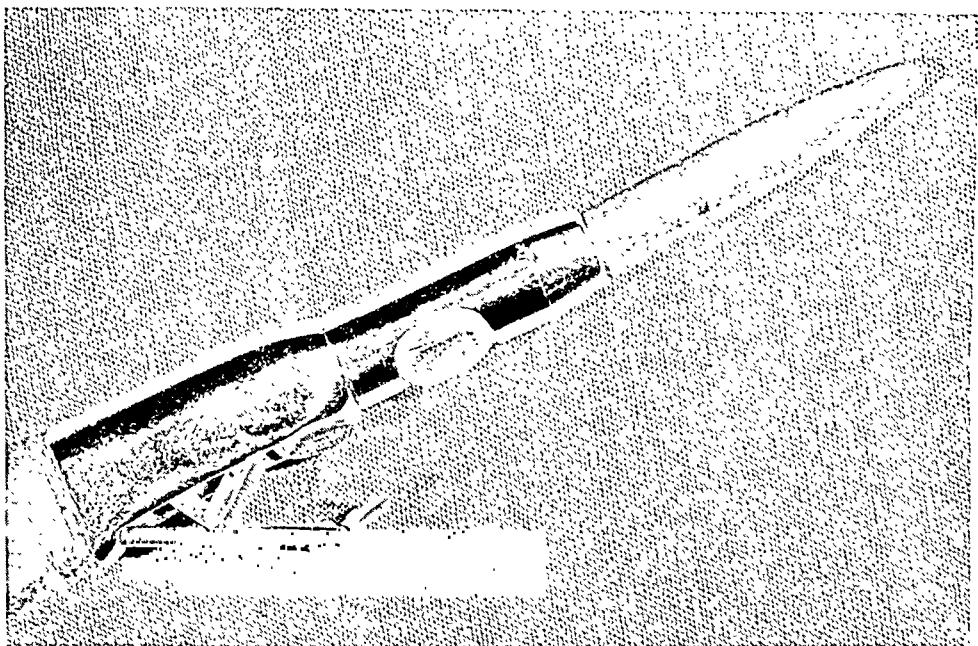


FIG. 4

the assistance of one of our most experienced manufacturers, I believe this has been accomplished.

The new instrument is essentially like the present flexible gastroscope with rigid proximal portion and flexible distal portion. An additional channel is provided through which a plastic suction tube may be introduced for aspirating secretions (Fig. 1). After removing the aspirating tube, the biopsy forceps are then passed through the same channel (Fig. 2). The proximal end of the instrument is shown in Fig. 3 with an adjustable eyepiece for fine focussing. The double thumb screw shown to the right of the eyepiece is for raising or lowering the "lid" or elevator. The purpose of the elevator is to aid in directing the biopsy forceps. The connections for air insufflation and electric cord are shown just to the right of the thumb screw. To the right of these connections the forceps are seen entering the special channel through a rubber stopper to prevent the escape of air. In Fig. 4 a close-up view is obtained of the distal end of the gastroscope with the forceps in the open position, elevated by the "lid", and in position to be seen through the objective lens. The light bulb and rubber finger tip are constructed in the usual manner.

Practical experience with this instrument is so far limited to only a few cases, but in spite of its slightly increased diameter, it has been passed without difficulty and satisfactory biopsies safely obtained. Until further refinements are made, it will probably be possible to obtain biopsies only in favorable cases with accessible lesions. However, the development of this instrument marks an important step in the right direction.

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# COMBINED LIVER BIOPSY AND LIVER FUNCTION STUDY IN 132 CASES OF CHOLELITHIASIS AND 31 CASES OF PEPTIC ULCER. (OPERATED CASES)

(EMPHASIS UPON EARLY MICROSCOPIC LIVER DISEASE AND  
PARTICULARLY ACUTE INFILTRATIVE HEPATITIS AND  
MICROSCOPIC PERIPORTAL CIRRHOSIS)\*

JOHN G. MATEER, M.D., FRANK W. HARTMAN, M.D., JAMES I. BALTZ, M.D., LAURENCE D. FALLIS, M.D., ARTHUR B. McGRAW, M.D., AND HUGH H. STEELE, M.D.

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## INTRODUCTION

This study is a sequel to previously published work<sup>1, 2, 3, 4</sup> dealing with the improvement of the normal standards and sensitivity of liver function tests and with the evaluation of their relative sensitivity, interpretation and practical use in subclinical and clinical cases. This report is an amplification of a recent *preliminary* combined study<sup>5</sup> of liver function and liver histology. It includes many additional cases, as well as a subgrouping of cases for comparative study. The fact that over twice as many cases are included here as in the *preliminary* study adds greatly to the statistical value and reliability of the observations and conclusions.

Recently interest has developed in attempts to correlate the positive results of various liver function tests with histological liver biopsy findings in different types of *well-developed* liver disease. Interesting contributions have been made by Hoffbauer, Evans and Watson<sup>6</sup>; Volwiler and Jones<sup>7</sup>; Popper, Steigman, Meyer, Kozoll and Franklin<sup>8</sup>; Sherlock<sup>9</sup> and Gillman and Gillman<sup>10</sup>.

In the following study the histological liver biopsy findings in two subgroups of patients with cholelithiasis and peptic ulcer, respectively, and with very *early* liver disease have been carefully studied and summarized. In addition to the numerous cases of microscopic periportal cirrhosis demonstrated, a type of microscopic acute hepatitis differing from acute necrotic hepatitis, and not previously emphasized in the literature, has been noted and described.

The incidence of positive liver function tests and the degree of positiveness of these tests of varying sensitivity have been noted, both in the cases of cholelithiasis and peptic ulcer. An attempt has been made to correlate the

\* Read at the annual meeting of the American Gastroenterological Association, April 30, 1948, Atlantic City.

histological findings with the results of the tests conducted upon the same patients.

#### CLINICAL AND GROSS PATHOLOGICAL MATERIAL UTILIZED

In 132 cases of cholelithiasis and 31 cases of peptic ulcer laparotomy was performed for correction of the above conditions, and during operation a liver biopsy was obtained in each case. The livers of most of the total 163 cases appeared *grossly normal* at operation. The remaining cases showed some gross scarring of the surface of the liver or a granular appearance.

Of the total 163 cases 121 presented no alteration from normal in the size of the liver on physical examination, no jaundice and no other preoperative *clinical* evidence of *liver* disease. The average age of the 132 patients with gallstones was 52 years and of those with ulcer 51 years.

#### COMPARISON OF LIVER BIOPSY FINDINGS IN A DEEP WEDGE FROM EDGE OF LIVER WITH NEEDLE BIOPSY TISSUE

In view of the fact that liver tissue adjacent to the gallbladder area is not representative histologically of the remainder of the liver, all liver biopsy tissues were obtained from areas far *distant* from the attachment of the gallbladder. Most of the liver biopsies were obtained from the lateral portion of the right lobe, but some were obtained from the left lobe of the liver.

The innermost portion of a wedge-shaped block of liver tissue about 1 cm. deep and excised from the edge of the liver was compared microscopically with hepatic biopsy tissue obtained simultaneously during laparotomy by deep needle puncture. A Vim-Silverman needle was employed in obtaining the first 25 needle biopsies and a Turkel needle†, a new and improved trephine type of needle, was used in obtaining the last 30 needle biopsies. (The edge of the needle biopsy tissue is less ragged with the Turkel needle than with the Vim-Silverman needle.) A "wedge" biopsy was obtained in every one of the 163 total cases studied, as contrasted with the 55 needle biopsies. All biopsy tissue was placed promptly in formalin to prevent postmortem changes.

We prefer the wedge biopsy to the needle biopsy since the former affords an examination of a more extensive area of hepatic tissue. It appears to provide a somewhat more representative picture of the hepatic parenchyma and stroma as a whole. Comparing the more extensive area of the "wedge" biopsy with the narrow strip of "needle" tissue in 55 cases, we found on an average of less than one plus more fibrous tissue in the stroma of the "wedge" biopsy than in the stroma of the "needle" biopsy. In this connection the

† Needle described by Turkel and Bethel: Jour. Lab. and Clin. Med., 28: 1246, 1943. This Turkel Trephine needle may be purchased from the Trefine Instruments Co. Inc., 1302 Industrial Bank Bldg., Detroit 26, Michigan.

practical question is as to which type of biopsy tissue offers the more accurate index of the stroma in the liver as a whole. The fact that in some cases the edge of the "needle" biopsy strand of tissue is somewhat ragged suggests that the needle may evade some of the tougher fibrous tissue instead of cutting it out cleanly as it is encountered. Several workers in this field with extensive experience with liver biopsy technique have noted that the needle may be deflected away from the thickened, tough, fibrous tissue of cirrhotic livers toward the much softer parenchymal tissue. Sherlock<sup>9</sup>, in analyzing 264 aspiration liver biopsies and in recommending the procedure, at the same time states that, "In cirrhosis the tough liver is difficult to pierce and a few liver cells may be extracted leaving the fibrous framework behind." Although recommending trocar liver biopsy as a diagnostic procedure of real value, especially in diffuse hepatic disease, Volwiler and Jones<sup>7</sup>, in enumerating several of its limitations, state that, "In coarsely nodular toxic cirrhosis a needle biopsy may fail to include scar tissue though the specimen is seemingly sufficient in amount." Since the question whether scar tissue is adequately removed by needle biopsy is a controversial point, however, and inasmuch as some authors feel that "wedge" biopsies tend to show slightly more scar tissue than is present in the depth of the liver, we have made allowance for this point in interpreting the significance of the exact thickness of the fibrous stroma of "wedge" biopsy tissue, as noted in our discussion below of the microscopic findings in "wedge" biopsies. We agree with others that needle biopsy tissue, if skillfully obtained, is quite satisfactory on the whole. Needle biopsies have the advantages that 1, they can be taken thru the abdominal wall and do not require a laparotomy or peritoneoscopic examination to obtain them and 2, serial needle biopsies can be obtained from patients under treatment, with follow-up observations of histological progress. We have preferred, however, studying wedge biopsies from laparotomy cases to needle puncture of the liver thru the abdominal wall, since we have been reticent about subjecting our patients to even one chance in 200 or 300 of a serious accident, such as uncontrolled hemorrhage, which may result from this diagnostic procedure.

#### HISTOLOGICAL HEPATIC FINDINGS—TYPES AND DEGREES (IN 132 CASES OF GALLSTONES AND 31 CASES OF PEPTIC ULCER)

The histological diagnoses of the liver biopsy material in these two groups of cases are summarized and compared in Table I.

Using the liver of a healthy child as a normal histological standard, a total of only 10 of the 163 cases presented a normal liver on histological study. The livers of human middle-aged adults, like the kidneys and other organs, usually show some deviation from normal.

It should be noted that the seven histological findings outlined and described in Table I occur in patients who have one or the other of two primary inflammatory conditions which occur in organs whose blood supply drains into the portal circulation.

Fifty-four per cent of the larger subgroup of 132 cases of gallstones presented at least one and usually two of the three following types of parenchymal cell abnormalities: (a) fatty infiltration, (b) vacuolation or (c) bile staining. Of these 132 cases 16% showed fatty infiltration of the parenchymal cells, 38%

TABLE I  
*Comparison of Histological Findings in Two Groups of Cases\**

HISTOLOGICAL DIAGNOSES	132 CASES GALLSTONES	31 CASES P. ULCER
	%	%
(1) Histologically Normal Liver.....	6	7
(2) Hepatosis (Reversible parenchymal changes e.g. vacuolation, bile-staining or fatty infiltration of cells. No stromal changes.).....	2	3
(3) Minimal Stromal Changes (Slight increase in periportal fibrous tissue and slight mononuclear infiltration).....	41	48
(4) "Microscopic Periportal Cirrhosis" (Definite + or ++ increase in periportal fibrous tissue and 1 or 2 plus mononuclear infiltration. May be parenchymal changes also.).....	33	29
(5) Biliary Cirrhosis (Micro) (Dilatation of bile ducts plus findings of periportal cirrhosis).....	2	0.0
(6) "Acute Infiltrative Hepatitis" (Microscopic) (P.M.N. cells in parenchyma, particularly around central veins. No necrosis of parenchymal cells).....	15	10
(7) Chronic Passive Congestion. (Microscopic dilatation of sinusoids).....	0.7	3

\* 54% of 132 gallstone cases presented at least one and usually two of following types of parenchymal cell abnormalities, namely, fatty infiltration, vacuolation or bile-staining of cells. 93% of 132 cases presented at least slight stromal changes.

68% of much smaller group of ulcer cases showed at least one parenchymal cell abnormality.

vacuolation and 39% bile staining of these cells. In 90% of these 132 cases there was either slight or moderate increase above normal of the periportal fibrous stroma.

Three of the seven histological findings referred to in Table I warrant some special discussion.

(a) The cases with "microscopic periportal cirrhosis" are defined as cases exhibiting 1, at least one and usually two plus increase above normal of fibrous tissue in the "wedge" biopsies, in addition to 2, definite one or two plus infiltration of the stroma with mononuclear cells. In the *needle* biopsy tissue these cases of periportal cirrhosis exhibit a definite mononuclear infiltration of the stroma and usually a one plus increase of fibrous tissue. In some cases

a two plus increase of fibrous stroma was present in the needle biopsy tissue. These cases apparently represent approximately the earliest stage of typical microscopic periportal cirrhosis.

Microscopic periportal cirrhosis occurred in 29% of the subgroup of peptic ulcer cases and in 33% of the subgroup of cases of cholelithiasis. This 33% incidence of early microscopic cirrhosis in the cases with gallstones, in association with the fact that gross cirrhosis of the liver occurs in a much smaller per cent of patients seen, indicates that many of these cases with "microscopic periportal cirrhosis" do not proceed to the subsequent development of macroscopic cirrhosis. On the other hand, gross cirrhosis, when it occurs, must have started in an early stage similar to that noted in the above cases. In fully developed cirrhosis the two essential microscopic findings upon which the diagnosis rests are the same as those upon which the microscopic early diagnosis rests, that is, 1, increase of stromal fibrous tissue and 2, mononuclear infiltration of the stroma.

It should be noted that as yet one cannot draw any final deductions about the exact relationship between microscopic periportal cirrhosis on the one hand and chronic gallbladder disease or peptic ulcer on the other hand. We hope next to obtain a control group of cases by studying the histologic findings in the livers of a group of patients presenting no associated organic disease in the gastrointestinal tract. It will be interesting to compare the incidence of microscopic periportal cirrhosis in such a group with that in the above groups of cases.

(b) In the large group of cases presenting "minimal stromal changes", in the "wedge" biopsy tissue there was usually only a one plus increase of fibrous tissue and a one plus infiltration of the stroma with lymphocytes. In about half of these cases the fibrous stroma in the *needle* biopsy specimens did not seem definitely thickened, whereas in the other half there was only one plus thickening of the stroma. This group of cases, therefore, should be differentiated from those with definite "microscopic periportal cirrhosis" as described above.

(c) The most interesting histological group is that including cases of "acute infiltrative hepatitis". This type of acute hepatitis, to which we have given the above name, has not been emphasized previously in the literature. It is characterized, in contrast to acute degenerative or necrotic hepatitis, or acute infectious hepatitis, by 1, the absence of necrosis and disintegration of the parenchymal cells and 2, by the presence of slight, moderate or marked infiltration of the parenchyma with polymorphonuclear cells. The latter cells are frequently arranged in a circlet about the central vein of the lobules, although they may be distributed throughout the parenchyma. Some of the polymorphonuclear cells appear within the parenchymal cells, and others are obviously extracellular. In these cases, practically no segmented cells are



PLATE I

R. D., Path. #89481. Photomicrograph—Medium Power  
Liver—Periportal area showing early fibrosis and round cell infiltration, vacuolar degeneration and  
fatty change in liver cells  
Early Periportal Cirrhosis

located in the periportal stroma, and only occasional cells of this type are located in the capsule of the liver. The number of segmented cells varied from one to three plus.

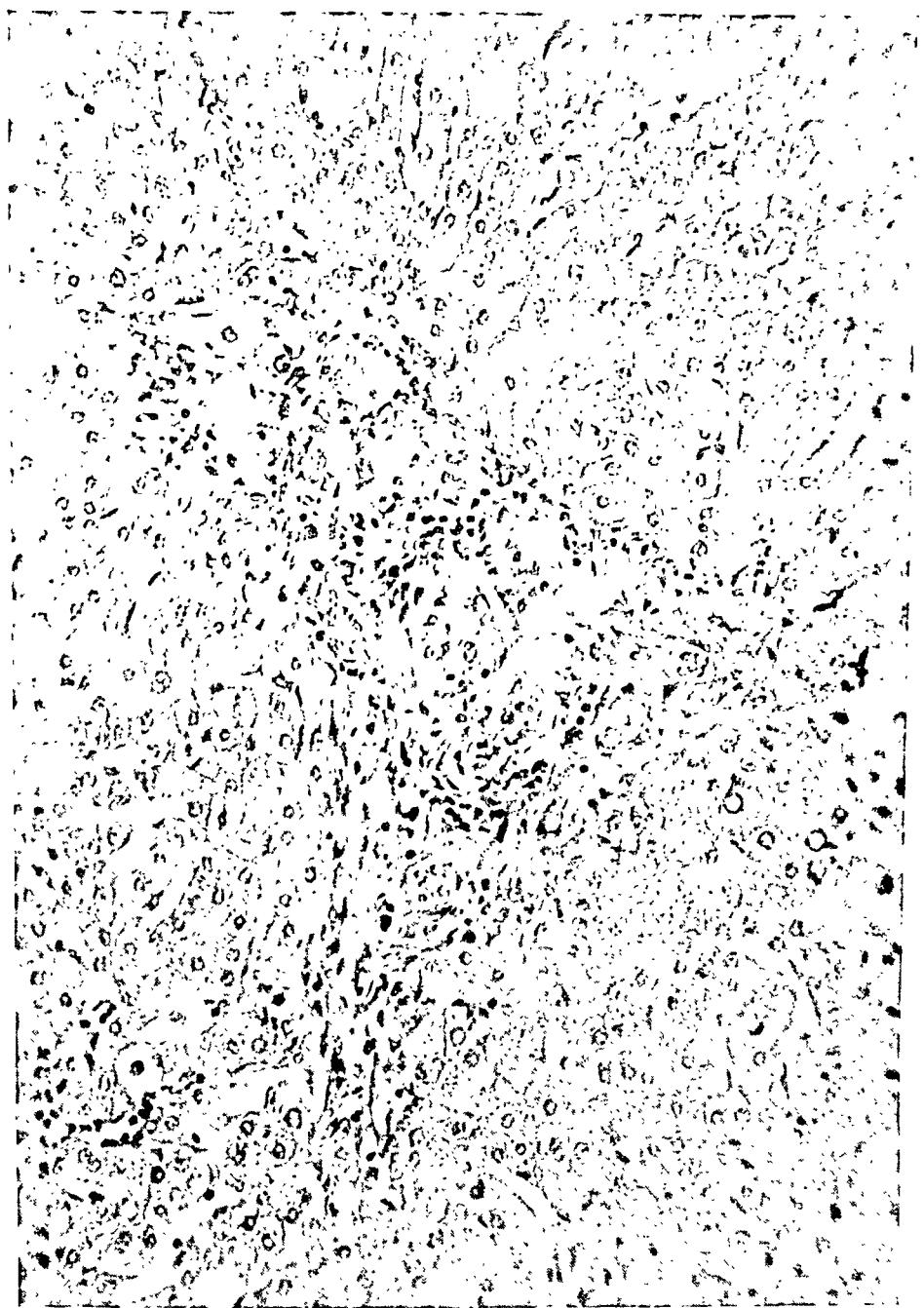


PLATE II  
I. L., Path. #93371. Photomicrograph—Medium Power  
Liver—Periportal area showing round cell infiltration and early fibrosis  
Minimal Periportal Changes

It is interesting to note that of the large group of cases with cholelithiasis 15% revealed this type of "acute infiltrative hepatitis". It should also be noted that this same type of acute hepatitis was present in 10% of the peptic ulcer cases, a smaller but, nevertheless, appreciable percentage of cases.



## PLATE III

J. L., Path. #91365. Photomicrograph—Medium Power  
Liver—Extensive and diffuse polymorphonuclear infiltration with vacuolar degeneration of liver  
cells and absence of necrosis  
Acute Infiltrative Hepatitis

As to the significance of this infiltrative type of acute hepatitis, the probability must be seriously considered that this condition is either secondary to infection and inflammation in the wall of the gallbladder or to inflammatory

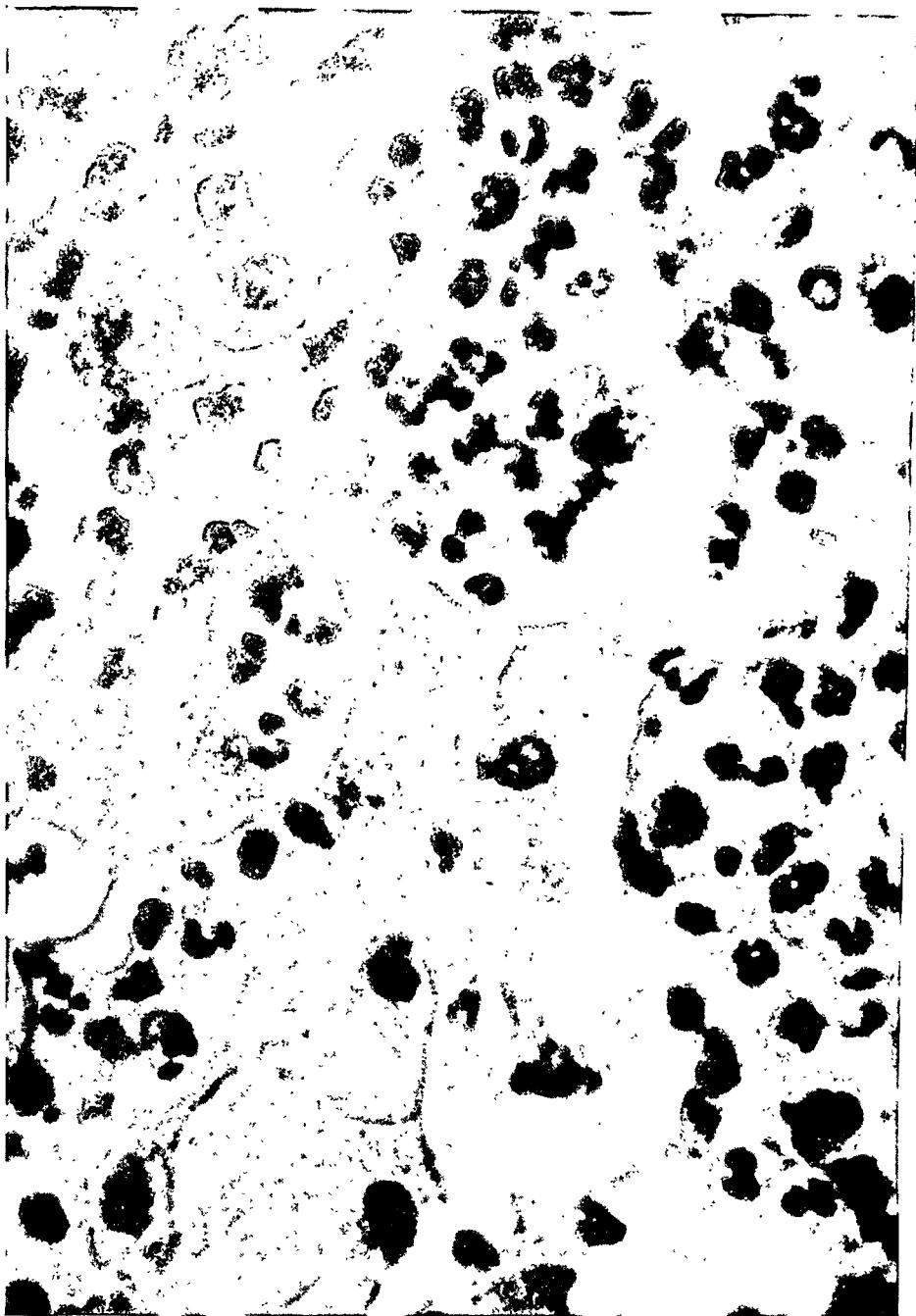


PLATE IV

J. L., Path. #91365. Photomicrograph—High Power (Same Case as Plate III)  
Liver—Extensive and diffuse polymorphonuclear infiltration with vacuolar degeneration of liver  
cells and absence of necrosis  
Acute Infiltrative Hepatitis

reaction about the base of the peptic ulcers. As evidence for this probability, 7 of the 20 cases with gallstones and acute hepatitis showed segmented cells (one plus to four plus) in the wall of the excised gallbladder. Furthermore,

all of the 20 cases with gallstones and acute hepatitis showed mononuclear infiltration of the wall of the gallbladder with fibrous thickening and evidence of chronic cholecystitis. Also, 80% of these 20 cases of acute hepatitis associated with gallstones had had multiple attacks of gallstone colic; and 20% had had low grade daily fever before operation, (99°–100°), not explained by any condition outside of the gall tract. Forty per cent of these 20 cases showed leucocytosis. (9,000 to 16,000 white blood cells.)

Of the three operated cases of peptic ulcer with associated acute hepatitis it seems likely that infection from the inflammatory reaction about the base of the ulcer may have reached the liver through the portal circulation, and, thus, been a contributing factor to the acute hepatitis. All three of these cases revealed an appreciable degree of scar tissue reaction about the base of the ulcers.

A less probable explanation of the acute hepatitis in these two groups of cases is that this condition might have been secondary to bacteria from some remote focus of infection. However, very few of these 23 total cases of acute hepatitis presented any evidence of such distant focal infection.

In the various histological subgroups of the total 163 cases, it is important to emphasize that the histological liver impairment is of a very early type. Five operated cases of gallstones with gross hepatic cirrhosis were omitted from the otherwise consecutive group of 132 operated cases of cholelithiasis.

#### RESULTS OF VARIOUS LIVER FUNCTION TESTS IN 132 OPERATED CASES WITH GALLSTONES AND 31 CASES OF PEPTIC ULCER

These results are outlined in detail in Table II. Six liver function tests in all were employed. An average of 4.4 tests were conducted upon each of the 132 cases of gallstones, and an average of 4.8 tests were conducted upon each of the 31 cases of peptic ulcer. Since all of the six tests were not conducted upon all the cases in each group and, therefore, were not carried out upon identical cases, no accurate deductions can be drawn from this table regarding the relative sensitivity of these tests. The matter of relative sensitivity has been studied and noted in our previous publications in which the same group of tests was performed upon identical cases. (In Table II the bromsulphalein and urobilinogen tests particularly appear relatively more sensitive than they really are.) Normal standards determined in our previous studies<sup>1, 2, 3, 4</sup> were employed in interpreting the results of these tests. The relatively high incidence of positive liver function tests in the cases with gallstones is not surprising. In our previous studies another group of cases with gallstones was studied with a group of the more sensitive liver function tests, and it was demonstrated that about 50% of that group of cases yielded positive results with at least one of the tests employed. The rather high incidence of positive tests in the ulcer group should also be noted.

The photoelectric, 45 minute 5 mg. per kilo bromsulphalein test is the most sensitive of the six tests employed. In previous liver function studies upon unselected identical cases with cirrhosis and cholelithiasis, in which studies the relative sensitivity of various tests was accurately demonstrated, it was apparent that the bromsulphalein test was definitely more sensitive than the cephalin and thymol tests. In this study the greater sensitivity of the bromsulphalein test appears to be even more pronounced.

TABLE II

*Results of Various Liver Function Tests in 132 Cases of Cholelithiasis and 31 of Peptic Ulcer (22 Duodenal; 7 Gastric and 2 Jejunal Ulcers)*

TYPES OF TESTS EMPLOYED* **	NO. PTS. TESTED*		% POSITIVE TESTS**	
	G. Stones	Ulcer	G. Stones	Ulcer***
(1) Bromsulphalein Test (45 min., 5 mg. per kilo Photo. method)†.....	82	26	34	38
(2) Ceph.-Chol. Floc. Test.....	123	31	13	26
(3a) Thymol Turbidity Test (Reduced pH of 7.55—doubling sensitivity)‡.....	123	31	13	13
(b) Thymol Flocculation Test.....	121	31	12	13
(c) Either Pos. Thymol Turb. or Floc. Test or both.....	123	31	15	16
(4) Quant. Urinary Urobilinogen Test (2 hr. collection of urine).....	72	11	28	9
(5) Serum Albumin Results.....	74	23	16	13
(6) Blood Prothrombin (Quick) (Normal Standard—reading above 50%).....	109	27	1	0.0
% of Pts. with one or more Pos. tests.....			62	48
% of Pts. with two or more Pos. tests.....			29	36

\* Average of 4.4 tests done upon each patient (583 tests—132 pts.).

\*\* No accurate deductions can be drawn from this table about relative sensitivity of tests. Six tests not done upon all identical cases.

\*\*\* Ulcer group of fewer cases is less significant statistically.

† B.S.P. test was not conducted upon jaundiced patients.

‡ Thymol turbidity results above 2 units are positive.

In our recent comparative liver function studies upon *identical* cases, the quantitative urinary *urobilinogen* test (with 2-4 P.M. urine collection) exhibited about the same sensitivity as the cephalin test and the modified thymol test with a pH of 7.55 of buffer solution. In a similar recent study upon identical cases the serum albumin was less sensitive than the cephalin test.

The fact that we were unable to obtain all six tests upon all the cases having liver biopsies does not invalidate the attempt to correlate the results obtained from each individual liver function test with the hepatic histological findings in the same group of cases.

## DEGREE OF POSITIVENESS OF TESTS

As to the *degree* of the positive results of different tests, it is apparent from a study of Table III that these results are definitely positive, but only mildly so in these two groups of cases. Although the percentage *incidence* of positive tests is quite similar in the two groups of cases, the *degree* of positiveness of the tests is definitely greater in the group of gallstone cases than in the cases of peptic ulcer.

The argument is sometimes advanced that a different set of normal standards should be employed for middle-aged individuals than for young adults, since

TABLE III

*Average Degree of Positiveness of Positive Tests in 132 Operated Cases of Cholelithiasis and 31 of Peptic Ulcer*

LIVER FUNCTION TESTS	NORMAL STANDARDS	AVERAGE POSITIVENESS OF POSITIVE TESTS*	
		Gallstone Group**	P. Ulcer Group
B.S.P. (Photoelectric) (5 mg. per kilo)	Retained Dye	Retained Dye	
(a) 45 min. retention	(a) Below 4.0%	9.3%	5.0%
(b) 60 min. retention	(b) Below 2.1%	7.3%	3.7%
Cephalin-Chol. Floc.	Below 2+ (+ or 0)	2.8 plus	2.2 plus
Thymol Test (pH of 7.55)			
(a) Turbidity	(a) Below 3 Units	4.6 units	4.4 units
(b) Flocculation	(b) Below 2+	3.0 plus	2.7 plus
Quant. Urinary Urobilinogen (Watson)	Below 1.0 unit	2.3 units	1.93 units
Serum Albumin	Above 4.0 gms.	3.0 gms.	3.84 gms.

\* It will be noted that these tests, on an average, are only slightly altho definitely positive, using our normal standards determined by studying 40 normal young adults as subjects.

\*\* Degree of positiveness of tests is greater in gallstone group.

the *average* results of tests may be slightly different for the two age groups. This suggestion does not seem valid since a different standard for middle-aged people would not be a normal standard, but would simply indicate that certain of the middle-aged group no longer exhibit normal liver function, just as many of them no longer exhibit entirely normal hepatic histologic findings. Furthermore, the fact that many middle-aged people still do show normal liver function, according to the normal standard of *young* adults, is significant. We feel that certain of the liver function tests should remain sufficiently sensitive to detect *early* impairment of liver function, which then can be corrected therapeutically at a stage when there is as yet little impairment of structure.

ATTEMPTED CORRELATION OF RESULTS OF LIVER FUNCTION TESTS WITH  
HISTOLOGICAL LIVER BIOPSY FINDINGS IN 132 CASES OF  
CHOLELITHIASIS

The statistics related to this subject are outlined in Table IV. In endeavoring to correlate the results of liver function tests with the histological liver biopsy findings in these early cases, obviously any attempt to draw deductions from the presence or absence of *stromal* changes in relation to positive and negative tests is futile, because 92% of the total 132 cases exhibited at least some stromal increase of fibrous tissue and because only 8%, or 10 cases, appeared without such stromal changes. Furthermore, in view of the well known

TABLE IV

*Attempted Correlation of Results of Liver Function Tests With Parenchymal Cell Abnormalities in Group of 132 Patients With Cholelithiasis\**

COMPARISON OF RESULTS OF TESTS WITH PRESENCE AND ABSENCE OF PARENCHYMAL CELL ALTERATIONS FROM NORMAL***	PERCENTAGE OF CASES (VARIOUS TESTS)**				
	CCF	BSP	Ser. Alb.	Ur. Uro-Bil.	Thymol
(a) Of cases with + Parench. changes, test + in.....	12	40	22	35	17
(b) Of cases with no Parench. changes, test + in	8	33	12	25	17

\* Parench. changes—Vacuolation, fatty infiltration or bile-staining of cells (at least two changes were usually present where any were present).

\*\* Since 54%, or 71 patients, showed *parenchymal* cell changes and 46%, or 61 cases, showed no such changes, this presence of an appreciable number of patients in each subgroup makes it possible to attempt at least to correlate the microscopic parenchymal cell changes with positive results of liver function tests.

(Only one positive blood prothrombin result was obtained in the 132 cases.)

\*\*\* Since 92% of 132 cases showed slight *stromal* changes and only 8% no such changes, it is obviously futile to even attempt to draw any statistical deductions from any effort to correlate these two groups with positive tests. Furthermore, *stromal* changes are too slight in this group to reduce parenchymal cells appreciably and thus reduce function.

“safety factor” in the total number of liver cells, one cannot conceive of such relatively slight increases of fibrous tissue, as occur in most of these cases, decreasing the total number of liver cells sufficiently to reduce function or alter the results of the tests.

An attempt, at least, can be made to correlate the positive results of the tests with the *parenchymal* cell abnormalities, since a sizable group of 54%, or 71 cases, showed one or more parenchymal cell abnormalities, and another statistically adequate group of 46%, or 61 cases, presented no parenchymal cell abnormalities.

In Table IV 4 of the 5 tests exhibit an appreciably greater per cent of positive results associated with the presence of parenchymal cell abnormalities than

with their absence, the exact ratio varying with each test. However, in the individual case no deductions can be drawn from a positive test, since an appreciable number of positive results from tests were associated with the absence of any parenchymal cell abnormalities which could be seen microscopically. (See line (b) in Table IV). Therefore, in these early cases, with relatively slight although definite histological abnormalities, the liver function tests in the individual case provide definite information regarding liver function only.

Even in advanced cases there are many individual instances in which the results of various liver function tests are almost identical, and yet the hepatic histology is extremely different. Conversely, there are numerous instances in which the marked pathological findings are essentially the same, but the results of the tests are quite different. In other words, even in the presence of advanced liver disease in the individual case information regarding liver function and liver structure must be considered more or less as separate items of diagnostic value. Both of these diagnostic studies should enter into the final appraisal of the individual liver problem, where both types of evidence are readily available.

Each type of information has its value. As pointed out by Volwiler and Jones<sup>7</sup>, in most advanced cases liver biopsies afford the *more* reliable information regarding the exact type and degree of morphological impairment present and regarding the prognosis of such patients and their probable response to treatment. However, in the type of case in which there is evidence of marked impairment of liver function, afforded by results of the tests, but evidence of very little abnormal structure in the liver biopsy tissue, the tests afford much more valuable information about the need for therapy than the liver biopsies. Pathological physiology often is a precursor of pathological anatomy and should be corrected promptly wherever possible. In the majority of early subclinical cases we have demonstrated<sup>4</sup> that this is possible.

#### SUMMARY

(1) This study is a sequel to previous research upon liver function tests and is an amplification of a recent combined study of liver function and liver histology, including over twice as many cases and a subgrouping of these cases for comparative study. The additional cases add greatly to the statistical value and reliability of this report.

(2) In a large group of 132 operated cases of cholelithiasis and in a small group of 31 operated cases of peptic ulcer, observations have been made upon the histological liver biopsy findings in tissue obtained at laparotomy, the preoperative incidence of positive liver function tests of varying sensitivity and the degree of positiveness of these tests. An attempt is made to correlate the

histological findings with the results of the tests conducted upon the same patients. The average age of these 163 cases was 52 years.

(3) This is essentially a study of very early acute and chronic liver disease. At operation the great majority of the 163 livers appeared normal grossly. Of the total 163 cases 121 presented no preoperative clinical evidence of liver disease, such as alteration in the size of the liver, jaundice, etc.

(4) All liver biopsy tissue was obtained either from an area in the right lobe of the liver far distant from the attachment of the gallbladder, or from the left lobe. Histologically representative liver tissue was thus obtained.

(5) The interior of deep "wedge" biopsies from the edge of the liver has seemed to provide slightly more representative microscopic information than needle biopsies for the reasons outlined. Wedge biopsies were obtained in all 163 cases and needle biopsies in 55 cases. Serial needle biopsies through the abdominal wall afford valuable information regarding the exact type and degree of liver disease and its progress under treatment; but needle biopsies of this type do involve a slight but definite risk.

(6) In the histological study of liver biopsy tissue, as summarized in Table I, only 6% of the 132 cases of gallstones and 7% of the 31 ulcer cases revealed a histologically *normal* liver. Two microscopic conditions of particular interest were noted and described, namely, (1) "microscopic periportal cirrhosis" and (2) "acute infiltrative hepatitis".

The former condition, characterized 1, by a slight but abnormal increase in the fibrous stroma and 2, by a mononuclear infiltration of the stroma, occurred in 33% of the gallstone cases and 29% of the peptic ulcer group.

The most interesting finding was a condition which we have designated as "acute infiltrative hepatitis". This condition, in contrast to acute necrotic hepatitis, has not been previously emphasized in the literature. This type of hepatitis is characterized by the absence of parenchymal cell necrosis and by the presence of a definite polymorphonuclear infiltration of the hepatic parenchyma particularly. "Acute infiltrative hepatitis" seems to be a fitting term for this condition.

Of the 132 cases with gallstones 15% revealed microscopic evidence of acute infiltrative hepatitis; and 10% of the 31 cases of peptic ulcer revealed the same condition. The evidence is outlined suggesting that this type of acute hepatitis is probably secondary to infection and inflammation in the gallbladder wall in the 20 cases of gallstones associated with this condition. In the 3 cases of peptic ulcer with associated acute hepatitis the latter condition is probably secondary to infection and inflammatory reaction about the base of the ulcer.

(7) Of the 132 cases of cholelithiasis, 39% exhibited bile staining of the parenchymal cells, 38% vacuolation and 16% fatty infiltration. Of the 132 cases, 54% exhibited at least one and usually two of these parenchymal cell

abnormalities; and the other 46% showed normal parenchymal cells. Of the 132 cases, 92% showed some degree of abnormal thickening of the stroma.

(8) The percentage incidence of positive results of a group of six liver function tests of varying sensitivity in the 132 cases of cholelithiasis and the 31 cases of peptic ulcer has been outlined in Table II. The relatively high incidence of one or more positive tests is due to the fact that 6 tests were included in this study, including 4 of the most sensitive tests. (The non-sensitive prothrombin determination was positive in only one of the 132 early cases.)

(9) The degree of positiveness of the tests in the two groups of cases is outlined in Table III. These tests, on the average, are only slightly but definitely positive. The degree of positiveness of the tests is definitely greater in the cases of cholelithiasis than in the ulcer group.

(10) The results of our attempt to correlate the positive results obtained from the liver function tests with the presence and absence of parenchymal cell abnormalities in the 132 cases of cholelithiasis are outlined in Table IV.

(11) In the case of 4 of the 5 tests shown in Table IV there was an appreciably greater per cent of positive tests associated with the presence of parenchymal cell abnormalities than with their absence. This observation indicates a tendency in a large group of cases for positive tests to be associated more frequently with parenchymal cell abnormalities than with a normal parenchyma. In the individual case, however, no deduction regarding the parenchyma can be drawn from a positive test, since an appreciable number of positive tests are associated with normal parenchymal cells.

(12) Not only in this early group of cases, but also in cases of more advanced liver disease, in the individual case, liver function tests afford definite evidence regarding liver function only. Information regarding liver function and biopsy evidence regarding liver morphology must be considered more or less as *separate items* of valued diagnostic information, both of which should enter into the final appraisal of the individual liver problem, where both types of evidence are readily available. Each type of information has its value; and the relative value of these two diagnostic methods varies in different types of cases.

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## DISCUSSION

DR. LEON SCHIFF (Cincinnati, Ohio): I believe this study represents the largest correlation of liver biopsy as obtained by the Silverman needle with surgical biopsy, a matter of 55 cases.

Since one cannot forget the possible effect of anesthesia and trauma accompanying operation and that these biopsies were obtained at surgery, one wonders if it wouldn't be desirable for Dr. Mateer and his associates to perform needle biopsies of the liver two or three days before operation, and then again after operation, and see if any differences can be noted.

I think the work emphasizes the importance of the microscopic examination of the liver, since very frequently histologic abnormalities were noticed in the presence of a grossly normal liver.

I hope he will show us a slide demonstrating the so-called borderline cases which numbered some 40 per cent. Just what these cases have of significance, of course, remains for further study.

I should like to ask him several questions: One, if he has any ideas as to the etiology of this peculiar form of what he called acute infiltrative hepatitis, which he noted in 10 to 15 per cent of the cases, whether he observed any bleeding at the site of needle biopsy of the liver, or whether he observed any at the site of surgical biopsies.

I am struck by the frequency of abnormal bromsulphalein retention in absence of any morphological changes in the liver, and I wonder how he explains this fact.

DR. FRANZ J. INGELFINGER (Boston, Mass.): Dr. Schiff raises a very pertinent point and I have to qualify what has been published by us, and what I have said. If the patient is lying on a table and then is tilted upright without any effort on his part, then bromsulphalein removal seems to be impaired. But that is a maneuver which decreases blood flow by inducing stagnation of blood, at least in splanchnic areas. It is not the same thing as being upright and moving around. Hence, impairment of bromsulphalein removal produced by tilting a patient upright does not prove that

the bromsulphalein test is affected by position if the patient is standing, sitting, or walking in a normal fashion.

We are engaged in trying to determine by tests whether exercise, eating, or other activities affect bromsulphalein removal. I can't answer your question any more specifically than that.

DR. FRANK W. HARTMAN (Detroit, Mich.): I should like to show one lantern slide to answer Dr. Schiff's question about the minimal changes we speak about in 40 per cent of these cases.

(Slide) This is the best example we have of a microphotograph of minimal changes, and you see the small area of cirrhosis or fibrosis, with occasional lymphocytes. That lesion we didn't feel justified in speaking of as cirrhosis, but we speak of it as a minimal change. It probably is the earliest type of lesion that we could note at all.

(Slide) Now, regarding the acute infiltrative hepatitis, this is the section from a gallbladder wall showing the acute inflammatory process with polymorphonuclear cells with just an occasional bit of epithelium left, and the liver as seen here, with acute infiltration throughout, also marked vacuolar changes in the liver cells.

(Slide) This is another, high power, of that same liver, showing the polymorphonuclear infiltration and acute vacuolar and granular changes in the liver cells.

(Slide) Another gallbladder that shows very little acute infiltration with only some rounded-form infiltration in the wall.

(Slide) The liver here showed early periportal cirrhosis, but others showed acute infiltrative hepatitis also.

As to the etiology of this acute infiltrative hepatitis, I don't believe we can say anything conclusive. It is a lesion that as far as we know has not been described before, and the best answer I can give to the question is that it occurred in the twenty cases of gallbladder disease and in the ten cases of gastric ulcer. It apparently is associated with acute or subacute chronic lesions in the gastro-intestinal tract.

DR. JOHN G. MATEER (Detroit, Mich.): I wish to thank Dr. Schiff for his excellent discussion. The first point that he brought up referred to the possible effect of the anesthesia upon the liver. We tried to reduce any possible effect of this factor to an absolute minimum in the following way: We requested the surgeons to obtain liver biopsy tissue at the beginning of each gallbladder operation instead of at the termination; and ethylene gas and ether anesthesia were employed, so that the patients had had very little ether at the time when the tissue was removed. Furthermore, the tissue was immediately placed in formalin, instead of being transported in a dry tube to the laboratory. Postmortem tissue changes were thus avoided.

Dr. Hartman has shown you a photomicrograph of a borderline case with *minimal* chronic stromal changes, as requested by Dr. Schiff.

One more word about the probable etiology of acute infiltrative hepatitis. All twenty of the acute cases which were associated with gallstones showed definite evi-

dence of *chronic* inflammatory reaction, with mononuclear cell infiltration and increased fibrous tissue in the gallbladder wall. Seven of the twenty cases of acute hepatitis associated with gallstones showed a larger or smaller number of *polymorphonuclear* cells in the gallbladder wall. Four of these cases might be classified as *acute*, with a two, three, or four plus number of polymorphonuclear cells. The other three cases contained only occasional polymorphs and would probably be designated as *subacute* cases.

It is also interesting to note that 80% of these twenty cases had had multiple attacks of gallstone colic, and were not cases of latent gallstones. There was, therefore, considerable evidence of irritation and inflammation in the gallbladder wall in these cases of acute infiltrative hepatitis.

As to Dr. Schiff's questions about our observations with regard to bleeding following liver biopsies, the surgeons did not keep any definite statistics on this point. I am sure, however, that there were very few cases that showed any appreciable bleeding. I can recall their discussing several cases of needle biopsies where there *was* some temporary bleeding until a suture was inserted. That brings up the point of remote risk of serious bleeding with the needle biopsy method, which Dr. Schiff up to the present time, in doing four hundred cases, has not encountered. I know of no one else doing the ordinary type of needle biopsy who has a record like that. Most other men report a mortality from bleeding of anywhere from one in one hundred, to one in three hundred—mortality rate.

The last question inquired as to why we happened to obtain numerous positive bromsulphalein results in cases showing such slight morphological changes. This fact illustrates the point that we have tried to emphasize briefly, namely, that the investigation of liver physiology and liver morphology must be regarded as two *separate* types of studies, two separate types of information. While there was a greater percentage of positive results of liver function tests associated with the presence of parenchymal cell abnormalities than with their absence, there is dissociation of structure and function very frequently both in the early and in the late cases of liver impairment.

## THE GASTRIC MUCOSA AFTER VAGOTOMY FOR PEPTIC ULCER

### A GASTROSCOPIC STUDY\*

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#### INTRODUCTION

The present surgical treatment of peptic ulceration by section of the vagus nerves proximal to their distribution in the stomach and abdominal viscera was re-introduced by Dragstedt<sup>1</sup>. Since his report of the first series of patients so treated, numerous other reports and evaluations of this important therapeutic measure have been published<sup>2-11</sup>. These published reports as well as a number of others reflect well the present reaction of various clinicians to this operation. The consensus of clinical opinions to date suggests that the majority of patients with duodenal ulceration refractory to the usual medical regimes have obtained various degrees of symptomatic relief as a result of either vagotomy alone or more often vagotomy coupled with gastroenterostomy or pyloroplasty to eliminate the delay in gastric emptying so often seen after simple vagotomy. The mechanism for this relief of symptoms is not entirely understood<sup>4</sup>, but it is felt that the postoperative diminution of gastric acidity by the elimination of the psychic impulse, plus hypotonicity of the gastric musculature are important factors in producing the improvement usually seen.

Although the present reports have been in general encouraging, several observers have stated that it is as yet too early to establish the permanent nature of the clinical improvement observed in so many of the operated patients. This feeling has been expressed by Ruffin<sup>2</sup>, Jordan<sup>7</sup>, Eusterman<sup>8</sup>, Grimson<sup>9</sup>, Thorek<sup>10</sup> and Collins and Stevenson<sup>11</sup>. The effect of vagotomy on the gastrointestinal tract distal to the pylorus is not clearly understood, although it is known from anatomical and physiological studies that these cholinergic nerves probably have fibers extending in many cases to the level of the splenic flexure<sup>12</sup>.

To date, few reports have been published concerning the gastroscopic appearance of the stomach after vagotomy. Paulson<sup>13</sup> and Wolff<sup>14</sup> have reported briefly on this phase of the postoperative vagotomized stomach. Both of these authors have described a diminished motility of the antrum and pylorus in a majority of the cases seen. In addition, changes in the appearance

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of the gastric mucosa have been noted. These changes consist of hyperemia and in some cases an appearance of thinning out and friability of the membrane. These mucosal changes are not limited to any specific portion of the stomach wall. Wolff, in his report also has pointed out a loss of the usual gastroscopic landmarks and an alteration of gastroscopic orientation. He found retained particles of food present as long as 15 hours after the last feeding.

#### MATERIAL AND METHOD

In order to evaluate further the effect of vagotomy on the gastric mucosa, a series of 20 patients was studied gastroscopically. These patients were chosen in the Gastro-Intestinal and Gastroscopic Clinics of two large hospitals, one a Veterans Hospital, the other a large general hospital with an active clinic service. Eight of the patients in this series had transthoracic vagotomy alone. In 7 of these cases, the surgery was for duodenal ulceration refractory to medical management. One patient (M. F.) had a persistent gastro-jejunal ulcer following gastroenterostomy for duodenal ulcer 12 years ago. The remaining 12 patients all had vagotomy and either pyloroplasty or gastroenterostomy for refractory duodenal ulceration. (Tables I and II). In the entire series there are 11 patients who had one or more preoperative gastroscopic examinations. Postoperative examinations were made at intervals of from 3 to 12 months. In several cases, the postoperative examinations were repeated.

In all cases, examinations were made by the author and the findings were confirmed and discussed by other members of the clinics who served as observers. The gastroscopic examinations in all instances evaluated not only the state of the gastric mucosa from the standpoint of appearance but also the motility of the stomach.

Attempts were made to evaluate the clinical results of the surgery. A "good" result was interpreted on the basis of the patient's subjective improvement as well as his freedom from symptoms of either ulcer or surgical complications. In addition, patients able to tolerate normal diets were considered in the "good" result group. The "poor" result group includes those with persistent pain or distress, delayed emptying, bleeding and in fact all those patients who required continued postoperative medical care.

The pre- and postoperative maximum free acidity obtained after insulin hypoglycemia<sup>15</sup> is also tabulated in cases where this information is available. It is felt, however, that any accurate determination of free acid following gastroenterostomy is impossible due to the reflux of small intestinal contents into the lumen of the stomach. Unfortunately, all patients did not have gastrointestinal X-ray studies at the time of their postoperative gastroscopic studies. However, in cases where these studies were made, the findings are tabulated in terms of appearance of mucosa and gastric motility for the sake of comparison with the gastroscopic picture.

It should be pointed out that the surgery in these patients was performed by a number of different surgeons. In all cases there is evidence in the surgical specimens of definite nerve tissue. For the most part, patients chosen had been cooperative about pre- and postoperative studies, and only patients have been included who cooperated well for gastroscopic examination.

## RESULTS

In presenting the results of this study, it is felt advisable to consider the two groups separately. In a general way, the findings in both groups are similar but there are certain significant statistical differences. No attempt

TABLE I  
*Vagotomy alone*

PREOPERATIVE				POSTOPERATIVE						
Patient	Age	Free Acid	Gastroscopy	Result		Month P.O.	Free Acid	Gastroscopy		X-ray P.O.
				Good	Poor			Mucosa	Motility	
H. W.	55	6°	Superficial gastritis	Normal	+	4		Superficial gastritis	Pyloro-spasm	Pyloro-spasm
M. N.	51	45°			+	5	0°	Superficial erosive, Antrum	Normal	Gastric Dilatation
C. L.	55				+	10	20°	Normal	Atony	Retention
R. T.	50	51°			+	12	45°	Hypertrophic erosive	Normal	Normal
E. J.	50	10°			+	10	40°	Hypertrophic erosive, severe	Normal	Gastric Ulcer (Antral)
O. W.	45	104°	Superficial gastritis	Normal	+	3		Erosive superficial	Retention	Retention
						12		Hypertrophic erosive	Atony	
M. F.	56	70°	Hypertrophic gastritis	Normal	+	1	58°	Healed G.U., hypertrophic gastritis	Spasm	Retention
O. L.	43	30°	Stomal ulcer			10		As preoperative	Normal	Stomal ulcer
			Normal	Normal	+	11	27°	Antral and lesser curvature erosions	Normal	Normal

will be made to report each case individually, but in each group there are certain striking cases which merit brief abstracts.

#### A. Vagotomy alone. (Table I)

In this group, 4 patients had preoperative gastroscopic examinations. In one case the mucosa was normal. Two patients had gastroscopic evidence of chronic superficial gastritis most marked in the antrum. The fourth patient

had an easily visualized stomal ulcer surrounded by a severe degree of chronic hypertrophic gastritis.

In 4 patients of this group the appearance of the gastric mucosa following surgery was most striking. The mucosa appeared friable and superficial erosions were seen. The color of the membrane was deeper red than one sees normally, and in all 4 cases the texture of the membrane was roughened and cobble-stone in appearance. These changes were not limited to any portion of the stomach wall, but were found scattered. They were most marked and



FIG. 1

FIG. 1. E. J. Severe hypertrophic and erosive gastritis involving the antrum. There are several superficial erosions with some oozing of blood.

FIG. 2. E. J. Microscopic section taken near the pylorus showing the marked round cell infiltration into the submucosa with formation of lymphoid follicles.



FIG. 2

most easily seen on the greater curvature of the antrum and in the region of the angulus.

One patient in this group (E. J.) illustrated these changes to a striking degree. Following transthoracic vagotomy for a long standing duodenal ulcer, he continued to have indigestion, gas and epigastric burning. There was some food relief, and it was necessary for him to follow a strict dietary regimen. Ten months after surgery, follow-up X-ray studies revealed what appeared to be a pre-pyloric ulcer. Gastroscopy at this time revealed several superficial erosions in the antrum with oozing of blood. These erosions were surrounded by a coarsely granular mucosa which had such a marked appearance of infiltration that it was felt the lesion could not be differentiated gastroscopically from carcinoma (fig. 1). On the basis of these findings, a subtotal gastric resection was performed. The gross surgical specimen revealed

the erosions and marked hypertrophic gastritis with typical cobblestone mucosa but no evidence of carcinoma. Microscopic examination of this specimen confirmed this diagnosis (fig. 2). In the sections one can see a marked infiltration of round cells into the submucosa and muscularis mucosae to form lymphoid follicles. In addition, the areas of superficial erosion are seen.

In another case (R. T.) the patient, an alcoholic, gave us an opportunity to evaluate the resistance of his postoperative stomach to the trauma of a short drinking spree. Although he had insisted that his operation had given him marked symptomatic relief, in the ten months following he had at least 4 episodes of hematemesis. Gastroscopy 10 months after operation revealed a moderately severe mixed gastritis most



FIG. 3. R. T. Acute erosive gastritis following a drinking spree. This is superimposed on a chronic hypertrophic and erosive gastritis.

a. Large erosion on greater curvature of antrum with some oozing of blood. There are some hypertrophic gastritic changes.

b. Coarsely nodular hypertrophic gastritis on posterior wall. There is some free blood overlying the mucosa.

marked in the antrum. Both superficial and hypertrophic changes were seen and there were two small erosions on the greater curvature of the antrum. At this time his response to the Hollander insulin hypoglycemia test had returned to the pre-operative level. Within 24 hours of his discharge from the hospital following the postoperative studies, he was readmitted intoxicated and having hematemesis. The day following readmission gastroscopic examination was repeated. In addition to the previously noted changes of his gastric mucosa, one could now see multiple oozing superficial erosions in the antrum, on the angulus and along the anterior wall toward the lesser curvature (fig. 3).

Although vagotomy has been employed in the surgical treatment of stomal ulceration following gastro-jejunostomy<sup>9</sup>, there is no record of the duration of the healing

obtained. One patient in this series (M. F.) had a refractory stomal ulcer of about 12 years duration. This lesion was observed gastroscopically 2 days before a trans-thoracic vagotomy was performed. There was an associated severe chronic hypertrophic gastritis. Ten days postoperatively gastroscopic examination was repeated and at this time the ulcer had healed but the gastritis persisted. At the time of his discharge from the hospital X-rays confirmed the evidence that the ulcer had healed. Nine months after surgery the patient was again having his preoperative ulcer symptoms and he stated that he had been following a strict dietary regime to obtain any sort of symptomatic relief. X-ray examination again revealed evidence of a stomal ulcer, and gastroscopy revealed the ulcer as well as the same degree of chronic hypertrophic gastritis noted in the previous examinations (fig. 4).

Two female patients in this series (M. N. and O. L.) both obtained good symptomatic relief following surgery. However, in both cases postoperative gastroscopic examinations revealed hypertrophic and erosive changes, most marked in the antrum (fig. 5).

In general it is seen that in this series of patients who had vagotomy alone, only in one case was the gastric mucosa normal following surgery (Table III). 75% of the patients had postoperative erosive changes and one patient showed gastritic changes without erosions. Of this group, 4 patients had been gasteroscoped before surgery (Table IV). The gastric mucosa in three of these patients had undergone progressive changes. In the fourth a pre-existing superficial gastritis persisted unchanged.

Examination of Table V reveals that there is no correlation between the motility of the stomach wall as judged by the gastroscopic examination and the status of the mucosa, although it may be significant that the one patient with normal mucosa had diminished motility. From the standpoint of postoperative acidity (Table VI), it is seen that the gastritic changes in a majority of these cases developed in spite of a diminution of free acid.

#### *B. Vagotomy and Gastroenterostomy. (Table II)*

This group of 12 patients showed fewer gastroscopic changes following surgery than were seen in the patients who had only vagotomy. However, only 4 patients had normal appearing gastric mucosa at the time of these post-operative studies. It is known that the incidence of gastritis following gastroenterostomy is high. Schindler<sup>16</sup> attributes this postoperative gastritis to lack of rhythmical contractions of the stoma. Observation of a large series of cases at the Gastroscopic Clinic of the Veterans Administration Hospital<sup>17</sup> tends to confirm this fact. In a series of postoperative stomachs only 10% had normal appearing mucosa. Therefore, the finding of normal gastric mucosa in 33½ of this small series suggests that the ablation of vagus nerve impulses may favor better intrinsic rhythmic activity of the stoma.

In 3 of the patients of this group, erosive and hypertrophic gastritic changes

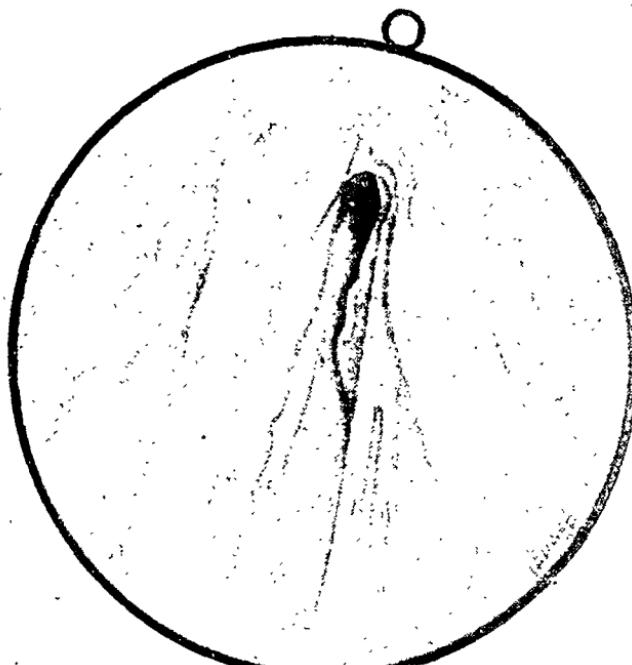


FIG. 4

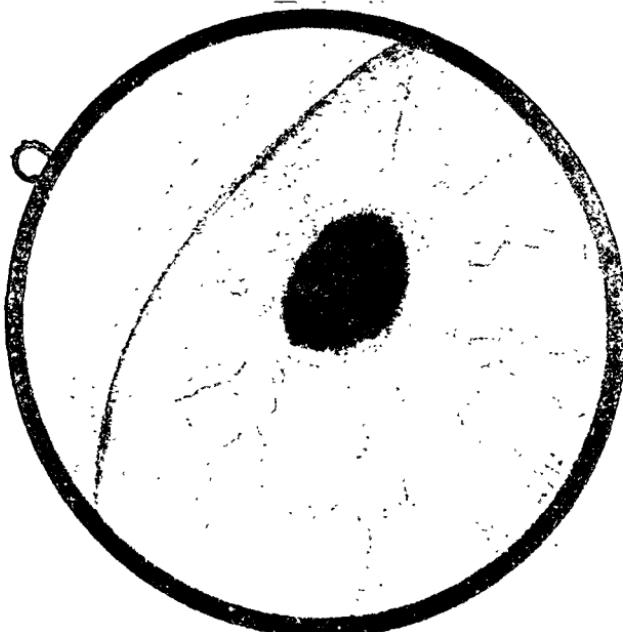


FIG. 5

FIG. 4. M. F. Anastomotic ulcer seen in profile. Examination 9 months after transthoracic vagotomy. There is a severe hypertrophic gastritis surrounding the stoma.

FIG. 5. O. L. Asymptomatic erosions of antral mucosa, seen 11 months after transthoracic vagotomy.

were observed which appeared similar to those noted in the other group. These changes were not limited to the area of the stoma but were also seen distal to

TABLE II  
*Vagotomy and Gastroenterostomy or Pyloroplasty*

Patient	Age	Free Acid	GASTROSCOPY		Result	POSTOPERATIVE					
						Good	Month P.O.	Free Acid	GASTROSCOPY		
			Mucosa	Motility					Mucosa	Motility	
L. J.	31		Normal	Spasm	+	8			Normal	Spasm of mid-body	
M. C.	68	20°			+	11			Hypertrophic gastritis, antrum	Decreased	
L. W.	37	65°	Superficial gastritis	Pyloro-spasm	+	8			Hypertrophic erosive	Spasm of mid-body	
W. P.	53	77°	Superficial gastritis	Pyloro-spasm	+	3	60°	Erosion	Spasm	Retention	
M. L.	60	70°				6			Normal	Normal	
J. S.	59	40°	Superficial gastritis	Atony	+	7			Normal	Normal	
L. R.	60	45°			+	4	30°		Hypertrophic erosive	Spasm	
C. S.	58	59°	Stomal gastritis, mixed form severe	Normal	+	12	0°		Hypertrophic (no erosions)	Atony	
J. F.	22	25°	Normal	Normal	+	6	60°		Atony	Normal	
E. B.	53	0°				10	30°		Normal	Pyloro-spasm	
A. W.	67					6	0°		Spasm	Normal	
W. M.	60	35°	Severe, superficial with erosions	Normal	+	8	20°	Pale, thin	Atony	?Polyp	
						3	5°	Superficial, no erosions	Atony	Normal	

it in the region of the angulus and antrum. An additional 2 patients had hypertrophic gastritic changes without evidence of erosion at the time of examination.

It will be noted that one patient (A. W.) had evidences of atrophy when examined. This is an elderly man who had followed an inadequate dietary regime following surgery. He had free acid on gastric analysis, but the X-ray impression of polyposis makes it necessary to follow his course carefully. The gastroscopic examination in this case failed to substantiate this X-ray finding.

One patient in this group (W. P.) has had three gastroscopic examinations since surgery. Three months postoperatively he was found to have an erosion of the angulus associated with some chronic superficial gastritis. At the time, no specific dietary regime was ordered for him. A repeated examination 3 months later showed complete healing of the lesions and a normal gastric mucosa. Within the past two weeks however, he has reported to the Clinic complaining that his ulcer symptoms

TABLE III  
*Postoperative Gastric Mucosa*

	NUMBER	PER CENT
Vagotomy alone (8 cases)		
Normal mucosa.....	1	12½
Chronic superficial gastritis.....	1	12½
Chronic hypertrophic gastritis.....	0	0
Atrophy.....	0	0
Erosions (6 cases 75%)		
With superficial gastritis.....	1	12½
With hypertrophic gastritis.....	4	50
Without gastritis.....	1	12½
Vagotomy and gastroenterostomy or pyloroplasty (12 cases)		
Normal Mucosa.....	4	33½
Chronic superficial gastritis.....	2	16½
Chronic hypertrophic gastritis.....	2	16½
Atrophy.....	1	8½
Erosions (3 cases 25%)		
With superficial gastritis.....	0	0
With hypertrophic gastritis.....	3	25
Without gastritis.....	0	0

have recurred. X-rays now reveal a definite stomal ulcer, and this could be observed at gastroscopy. There is an associated chronic superficial gastritis. It is significant that this patient attributes his relapse to marked anxiety concerning his daughter who has recently had a psychotic episode and has been receiving shock therapy.

From the standpoint of change in the mucosa as seen gastroscopically (Table IV) it is seen that three patients showed improvement. In 2 cases, mucosa was unchanged and in 2 others the mucosal changes seen before surgery had become more severe.

The role of the rhythmic function of the stoma in preventing the development of gastritis following surgery is well demonstrated in Table V. Here it is seen that normal peristaltic activity was not seen in any of the patients with gastritic changes.

TABLE IV  
*Postoperative changes—Preoperative Gastroscopy*

	NUMBER	PER CENT
Vagotomy alone (4 cases)		
Improved.....	0	0
Unchanged.....	1	25
More severe.....	3	75
Vagotomy and gastroenterostomy (7 cases)		
Improved.....	3	42
Unchanged.....	2	29
More severe.....	2	29

TABLE V  
*Postoperative motility*

	NORMAL		INCREASED		DECREASED	
	Number	%	Number	%	Number	%
Vagotomy alone						
Mucosa normal.....	0	0	0	0	1	12½
Gastritis.....	5	62½	2	25	0	0
Vagotomy and gastroenterostomy						
Mucosa normal.....	2	16⅔	2	16⅔	0	0
Gastritis.....	0	0	3	25	5	41⅔

TABLE VI  
*Mucosa and postoperative acid*

	MUCOSA NORMAL		GASTRITIS	
	Number	%	Number	%
Vagotomy alone				
P.O. Acid increased.....	0	0	1	16⅔
P.O. Acid decreased.....	0	0	5	83⅓
P.O. Acid unchanged.....	0	0	0	0
Vagotomy and gastroenterostomy				
P.O. Acid increased.....	0	0	0	0
P.O. Acid decreased.....	1	14	3	42
P.O. Acid unchanged.....	1	14	2	28

Gastritis is associated with diminished motility in 41% and with increased motility in 25% of the cases. This is demonstrated in the case of L. W., who on postoperative examination was found to have a marked mid-body spasm associated with erosion and gastritic changes (fig. 6). It may be significant that this patient is a very tense

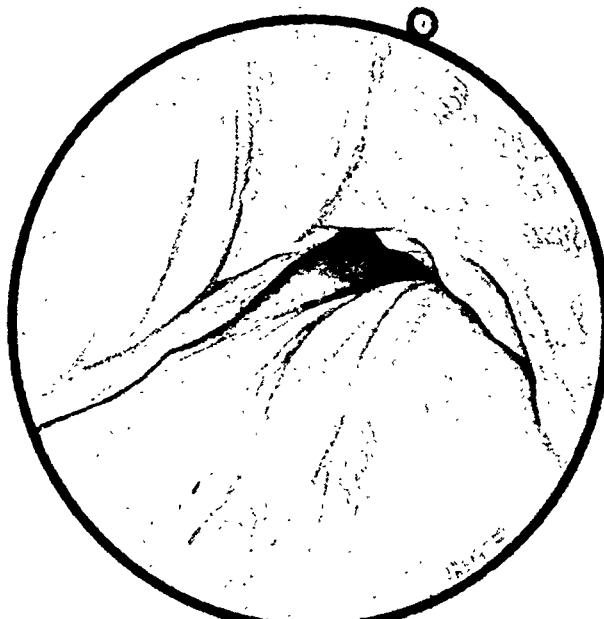


FIG. 6

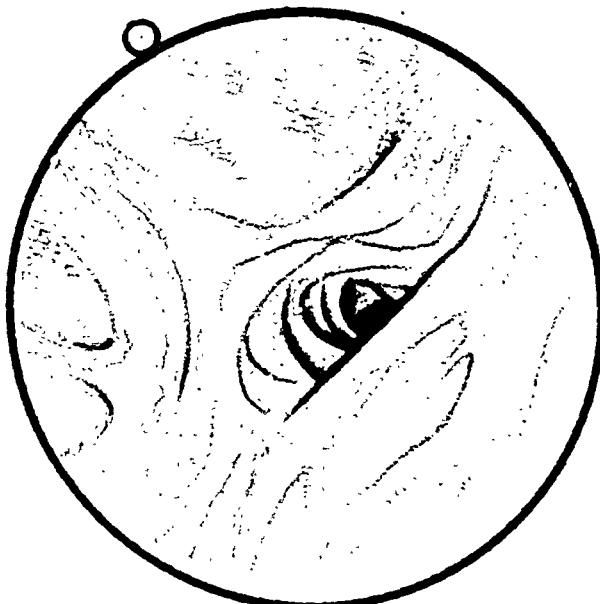


FIG. 7

FIG. 6. L. W. Superficial erosions of angulus associated with marked annular spasm of distal half of stomach.

FIG. 7. L. J. Marked annular spasm of mid body seen 8 months after transthoracic vagotomy.

individual, difficult to examine. At the time of his preoperative examination, a marked, prolonged pylorospasm was observed. In this case, vagotomy apparently had little effect on gastric motility. The two patients with gastroscopic evidence of increased motility and normal mucosa had less marked spasm.

It is difficult to make any clear-cut correlation of postoperative acidity and gastric changes in this series since, as stated before, the evaluation of gastric acidity following gastroenterostomy is not an accurate procedure.

One general observation which applies equally to both of these groups of patients is the finding that atony is not a constant result of vagotomy. It will be noted that in a number of patients, pylorospasm or midbody spasm was seen either at the time of gastroscopy or during the course of X-ray studies. In one case (J.F.) there was a prolonged period of cardiospasm following surgery which finally responded to dietary management and sedation. Similar instances have been reported by Moses (4). In 6 of the 20 cases atony was observed, and in these cases antral peristalsis was sluggish and the pylorus appeared patulous.

#### DISCUSSION

In this series of 20 patients who have been studied gastroscopically following vagotomy for peptic ulceration, definite abnormalities of the gastric mucosa have been observed in 15 cases. In the cases of simple vagotomy without gastroenterostomy gastritic changes have been seen in 75% of the patients examined; in the series in which a gastroenterostomy was done at the time of vagotomy changes are seen in the mucosa again in 75% of the patients, but in only 25% of this series are the changes at all severe. In addition to abnormalities in the appearance of the mucosa, abnormal motor activity has been observed in 13 cases. Seven of these patients had evidence of increased peristalsis; the other 6 appeared to have diminished peristalsis. In the cases of vagotomy without gastroenterostomy there seems to be no correlation between motor activity and postoperative gastritic changes. However, there does appear to be such a correlation in the gastroenterostomy series.

There is a predominant general pattern to the mucosal changes seen in this series of cases. This pattern consists of an appearance of chronic hypertrophic gastritis manifested by a coarsely granular or cobble-stone appearance of the gastric mucosa. This is not limited to any specific portions of the stomach wall, although it is most usually and easily observed on the greater curvature of the antrum and the region of the angulus. In one case (fig. 2) microscopic sections obtained when a subtotal gastric resection was performed 10 months after vagotomy confirmed the gastroscopic diagnosis of chronic hypertrophic gastritis. In a number of instances there was superficial (mucosal) ulceration associated with these hypertrophic changes producing a hyper-

trophic-erosive gastritis. There is no close correlation between the existence of these gastric changes and symptoms. However, in at least 3 patients there was bleeding at some time after the vagotomy and there are 2 instances of development of stomal ulceration with typical ulcer symptoms.

In addition to the changes in the texture of the mucosa certain cases revealed changes in the color of the mucosa. This color was usually a darker shade of red than is usually seen. The significance of this change is difficult to interpret in the light of the report of Wolf and Andrus<sup>18</sup> who were able to observe the gastric mucosa of a subject through a gastrostomy before and after vagotomy and found that in their case the color of the mucosa became more pale. It is not unlikely that this pallor may have been a transitory change. The post-operative observations in this case were only carried out for a brief period. It is my feeling that the color changes seen in so many of the operated patients in this series and reported also by Wolff<sup>14</sup> represent an alteration in the circulation.

Etiologic factors too numerous to mention have been described for chronic gastritis<sup>19,20</sup>. In this series there is one common etiologic denominator, the removal of the central cholinergic supply to the gastric mucosa. This is in turn associated with what appears to be an almost specific gastroscopic picture. It is well known that this interruption of innervation at least theoretically diminishes peristaltic activity of the hollow viscera as well as acid, pepsin and mucin secretion<sup>21</sup>. Whereas these results of vagotomy may favor the healing of typical chronic peptic ulcer, certain adverse effects may be produced by the operation.

Ivy<sup>22</sup> has pointed out that vagotomy leaves the vasoconstrictor and motor inhibitory fibers unopposed. In studies carried out by Boles and his associates<sup>23</sup> the correlation between peptic ulceration and abnormalities of the circulation was described. It is not unlikely that the unopposed vasoconstrictor state resulting from vagotomy produces in the wall of the stomach a condition of relative circulatory insufficiency similar from the functional standpoint to that described by Boles and ascribed by him to extragastric circulatory disorders of several types.

The role of mucin in maintaining the integrity of the gastrointestinal mucous membranes has been demonstrated by several investigators. In the case of the gastric mucosa, Babkin and Komarov<sup>24</sup> as well as Wolf and Wolff<sup>25,26</sup> have reported on this protective function of mucin. In their most recent report, Wolf and Wolff<sup>26</sup> stress also the dissociation between acid and mucin secretion. Mucin secretion is diminished by vagotomy and thus lowers the resistance of the gastric mucosa to direct trauma. Beazall and Ivy<sup>27</sup> demonstrated the development of peptic ulceration in the stomachs of vagotomized rabbits when fed a diet high in residue content. One of the patients in this series (R. T.) carried out a somewhat similar experiment by going on a short alcoholic spree which resulted in gastric erosions and hemorrhage. Another patient (W. P.) demonstrated the lowered resistance of his gastric mucosa probably as a result of acid-mucin dissociation, developing a marginal ulcer during

a period of anxiety and concern for his psychotic daughter. In cases of this sort it is not unlikely that histamine secretion is stimulated and this in turn produces the increase in acid and peptic activity<sup>22</sup>. In the case of the patient M. F., healing of his anastomotic ulcer was probably a result of bed rest and ideal medical care. On a general diet at home, the ulcer soon recurred in spite of vagotomy.

The fact that gastric changes are seen less frequently in patients who had gastroenterostomy at the time of vagotomy may be explained on the basis of the more rapid emptying of the stomach. As a result, physical trauma is not as prolonged as in the unoperated stomach.

Although it is known that interference with normal innervation of certain body structures produces atrophy, atrophic changes were seen in only one patient in this series. It is possible that the gastric changes seen in some of these patients may eventually become atrophic. Schindler<sup>23</sup> has reported this as a sequel to chronic superficial gastritis. Atrophy developing in the soil of a chronic hypertrophic gastritis has been seen by the author<sup>24</sup>.

#### SUMMARY

1. Vagotomy produces definite gastric changes in the gastric mucosa. These changes occurred in 75% of patients having vagotomy alone and in almost 50% of cases in which gastroenterostomy was done at the time of vagotomy. The mucosal changes most commonly seen consisted of hypertrophic gastritis not limited to any one portion of the stomach and frequently associated with superficial erosions.

2. It is felt that the changes which occur as a result of vagotomy influence the development of gastritis. These changes consist of: (a) altered circulation; (b) altered secretion of mucin together with dissociation of acid and mucin secretion; and (c) altered motility.

3. These changes perhaps reduce the resistance of the gastric mucosa to physical trauma. It is interesting to note, then, that the operation which primarily separates the gastric mucosa from psychic trauma makes it more susceptible to physical trauma.

4. It is impossible to correlate the changes seen with the degree of free acidity found after vagotomy. It is furthermore impossible in patients with gastroenterostomy to correlate these changes with the insulin test. In the patients who had vagotomy only, the gastric changes developed in spite of evidences by means of the insulin test, that the vagotomy had been complete.

5. The presence of a gastroenterostomy which functions well serves to protect the gastric mucosa from these traumatic factors by permitting more rapid gastric emptying and by permitting the reflux of alkaline small bowel contents. This factor accounts for the relatively smaller incidence of gastric changes in the cases in which a gastroenterostomy was done at the time of vagotomy.

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## ACUTE CHOLECYSTITIS

### CORRELATION OF BACTERIOLOGY AND MORTALITY\*

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#### INTRODUCTION

Many studies have been reported by various observers on the bacteriology of acute and chronic cholecystitis. Andrews and Henry<sup>1</sup> reported sterile cultures from the gallbladder in 68 per cent of patients with chronic gallbladder disease, 58 per cent of patients with acute gallbladder disease, 75 per cent of patients with stones but with a normal gallbladder wall, and in 87.5 per cent of patients with a normal gallbladder. Magner and Hutcheson<sup>2</sup>, in a comprehensive review, reported the contents of the gallbladder to be sterile in 65 per cent of all patients studied. Lester<sup>3</sup> reported that in patients with acute gangrenous cholecystitis cultures were sterile in 41 per cent, and in patients with acute nongangrenous cholecystitis the cultures were sterile in 72 per cent. While the presence of a positive culture does not necessarily denote bacterial infection, inasmuch as this is found occasionally in normal gallbladders, our study shows a direct correlation between the incidence of positive cultures and the duration of the disease, the morbidity of complications, and the mortality rate.

Bacterial studies were made in patients with acute cholecystitis who were operated upon on the University of California Surgical Service at the San Francisco Hospital during the 10 year period from 1936 to 1946. This hospital is a city charity hospital where disease processes are often encountered in an advanced stage. During this time it was possible to obtain bacterial studies on 160 patients with acute cholecystitis. On drainage of the acutely inflamed gallbladder, or shortly after its excision, its fluid content was aspirated and, together with a segment of the wall about 1 cm. square, was sent to the laboratory for aerobic and anaerobic cultures. In addition, cultures were obtained in 91 patients with chronic cholecystitis for comparison. Table 1 shows the results of bacterial cultures from 251 patients. It is coincidental that sterile cultures were obtained from exactly 43 per cent of both groups. The table shows the wide variety of organisms grown in pure and mixed culture. In those patients with acute cholecystitis, the colon bacillus in pure culture and associated with other organisms predominated; Staphylococci, Streptococci

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and anaerobes following in frequency in the order named. A host of other organisms were found only occasionally, which certainly suggests that some of them may not have been pathogenic.

The fluid content of the gallbladder was found to be sterile in 58 per cent of patients with acute cholecystitis, while the gallbladder wall was sterile in 49

TABLE 1  
*Bacterial cultures in 251 patients with gallbladder disease*

CULTURE RESULTS	CHRONIC CHOLECYSTITIS		ACUTE CHOLECYSTITIS	
	Number	Per Cent	Number	Per Cent
Negative.....	39	43	69	43
E. Coli (alone).....	8	9	29	18
E. Coli and Strep.....	3	3		
E. Coli and anaerobic cocci.....	2	2		
E. Coli and others.....	7	8		
E. Coli, anaerobes and Strep.....			14	9
E. Coli, anaerobes and Staph.....			3	2
E. Coli, Gram positive cocci.....			2	1
E. Coli, Welchii, Staph., Proteus.....			3	2
Hemolytic Staph.....	11	12	10	6
Nonhemolytic Staph.....	4	4		
Staph. and Strep.....	1	1	2	1
Beta Strep.....	1	1	2	1
Strep. Viridans.....	3	3	6	4
Diphtheroids.....	4	4	3	2
Friedlander's bacillus.....	1	1	2	1
Catarrhalis.....			2	1
Proteus.....	1	1		
Typhoid.....			2	1
Gram pos. rods (anaerobes).....	2	2		
Salmonella.....	1	1		
Pyocyanus and Diphtheroids.....	1	1		
Aerobic spores.....	2	2		
Anaerobes.....			2	1
Gram negative rods.....			2	1
Proteus, gas anaerobes, E. Coli.....			3	2
Gram neg. rods, Diphtheroids.....			2	1
Subtilis, Gram pos. cocci, Yeast.....			2	1

per cent. The incidence of sterility of both the content and the wall was 43 per cent.

The lowest incidence of positive cultures was 35 per cent during the first 24 hours of the onset of acute cholecystitis (Chart 1). The incidence then rose so that during and after the third day the percentage of positive cultures varied from 65 to 80 per cent. Those patients operated upon between the 11th and 35th days showed an incidence of positive cultures of only 46 per cent. During

this latter period the gallbladder inflammation was either subsiding or quiescent. Study of this chart suggests that the most favorable period for surgical intervention is either during the first three days or after the reaction in the gallbladder is on a downward trend or has subsided. This is borne out by a comparison of culture results shown in Table 2. The incidence of positive

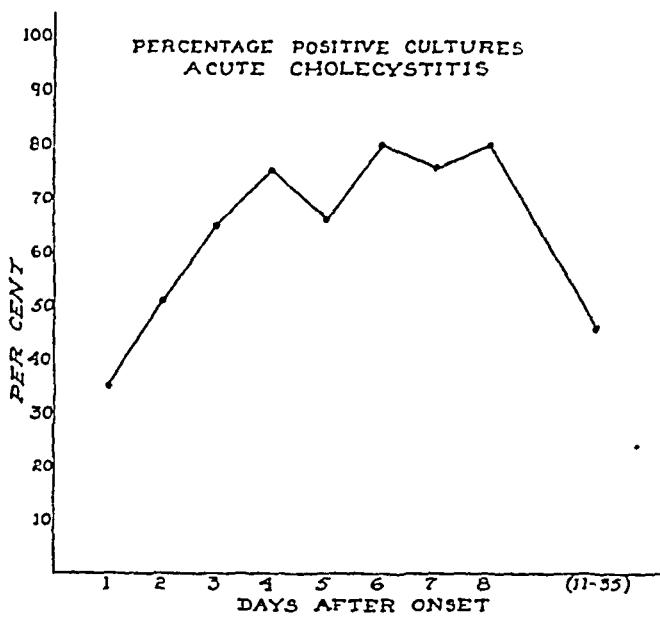


CHART I

TABLE 2  
*Culture results in 251 patients with gallbladder disease*

	NEGATIVE CULTURE	POSITIVE CULTURE
	%	%
Acute Cholecystitis.....	43	57
Chronic Cholecystitis.....	43	57
Patients Dying from Cholecystitis.....	21	79

cultures in the entire group was 57 per cent; in those patients who died following surgery the incidence was 79 per cent.

This comparison would suggest that there is a correlation between the incidence of positive cultures and the mortality rate. During the first three days of the attack when the incidence of positive cultures was at its lowest, the over all mortality rate was 3.2 per cent (Table 3), while between the fourth and eighth days of the attack the mortality rate rose fourfold to 12.8 per cent, and during the subsiding or quiescent period the mortality rate dropped to 4.4

per cent, approaching the low mortality that was encountered during the first three days. Patients operated on between the fourth and eighth days were taken to surgery because the symptoms, signs and laboratory data suggested that the inflammatory process in the gallbladder was progressing or perforation had taken place. There were ten patients with perforation of the gallbladder operated on in the 4 to 8 days period with five deaths, a mortality of 50 per cent for this group. The highest mortality rate for the series (16.2 per cent) was in those patients over 50 years of age who were operated on during the 4th to 8th day of the attack.

These bacterial studies explain the lack of signs of acute inflammation which may be seen histologically in sections of gallbladders showing acute cholecystitis. Whereas a small percentage of specimens may show marked polymorphonuclear leucocytic infiltration, and even abscess formation in the walls of the gallbladder, most specimens, particularly during the first three days of the disease, show marked edema and hyperemia with lymphocytic and eosino-

TABLE 3  
*Acute cholecystitis* (160 Cases)

DURATION OF ATTACK days	MORTALITY RATE (PER CENT)		
	Over 50 years of age	Under 50 years of age	Total
1-3	4.1	2.0	3.2
4-8	16.2	7.2	12.8
11-35	5.4	1.8	4.4

philic infiltration. As observed by McKibbin and McDonald<sup>4</sup>, there may be small groups of polymorphonuclear leucocytes which in themselves may not denote bacterial invasion. These authors also showed that the bacterial flora of normal and inflamed gallbladders were the same and they emphasize a noninfectious origin of acute cholecystitis.

In patients with histological evidence of acute gangrenous cholecystitis there may be found large groups of polymorphonuclear leucocytes infiltrating the area surrounding necrosis in the gallbladder wall. The occurrence of previous attacks will determine the presence or quantity of fibrous tissue in parts or all of the gallbladder wall. The relationship of the arterial and venous blood supply to the gallbladder wall may be a factor in the speed of development of acute gallbladder disease. Thickening of the gallbladder wall in acute cholecystitis is due mainly to edema of the outer layer. Thickening of the serosa with round cell infiltration, dilatation of the lymphatics and capillaries and the deposition of fibrinous exudate are common findings. The mucosa is often found to be normal.

In a correlation of the mortality with the type of operation (Table 4) it is seen that in four patients where just an abscess was drained the mortality rate was 50 per cent. The next highest mortality rate was in those patients who had cholecystostomy. Drainage of the gallbladder was performed in those patients who were elderly or poor risks when there was some contraindication to extensive surgery, such as the presence of an abscess, or when the build or obesity of the patient would have permitted cholecystectomy only with difficulty. It has been our feeling that in many of these elderly patients encountered at this type of hospital a cholecystostomy is still indicated and that more extensive surgery would result in an increase in mortality rate. In this series of 160 patients operated upon for acute cholecystitis the mortality rate

TABLE 4  
*Operative mortality*  
Acute Cholecystitis

OPERATION	NUMBER CASES	MORTALITY PER CENT
Cholecystostomy.....	51	15.7
Cholecystectomy.....	87	3.4
Cholecystectomy and common duct exploration.....	18	11.1
Drainage abscess.....	4	50.0
Total.....	160	9.3

TABLE 5  
*Acute Cholecystitis*

	OVER 50 YEARS OF AGE	UNDER 50 YEARS OF AGE	TOTAL
Number of patients.....	90 (56%)	70 (44%)	160
Deaths.....	12	3	15
Mortality Rate.....	13.3%	4.3%	9.3%

was 9.3 per cent. During the last three years of this period the mortality rate was 5.1 per cent.

Table 5 shows that out of 15 deaths in the series, 12 deaths occurred in patients over 50 years of age, with a mortality rate of 13.3 per cent in that group. The causes of death in the operated patients can be seen in Table 6. Septic complications accounted for 53.3 per cent of the total postoperative deaths, again indicating a correlation between the high incidence of positive bacterial cultures and the mortality rate. Six, or 40 per cent of the patients who died had a peritonitis, subphrenic or subhepatic abscess, and two, or 13.3 per cent, had a blood stream infection with positive blood cultures. This

would strongly suggest that even though bacterial invasion may play a secondary role in the etiology of acute cholecystitis, the high mortality rate, and high morbidity and liability to complications are associated with the presence of bacteria in the acutely inflamed gallbladder.

In an analysis of the extent of the disease (Table 7) it was found that in 127 patients or 80 per cent the process was limited to the gallbladder; in 10 patients, or 6.2 per cent, areas of gangrene were present; 10 patients, or 6.2 per cent, were found to have empyema of the gallbladder as recognized by its

TABLE 6  
*Causes of death in operated cases of acute cholecystitis*

	NUMBER	PER CENT
Peritonitis.....	6	40.0
Septicemia.....	2	13.3
Hepato-renal Syndrome.....	1	6.6
Pulmonary.....	2	13.3
Cardiac.....	2	13.3
Other Causes		
Hemorrhage 1; Anesthesia 1.....	2	13.3
Total.....	15	100

TABLE 7  
*Analysis of 160 operated cases of acute cholecystitis*

	NUMBER	PER CENT
Acute Cholecystitis.....	127	80.0
Acute Gangrenous Cholecystitis.....	10	6.2
Empyema of Gallbladder.....	10	6.2
Acute Gangrenous Cholecystitis with perforation and generalized peritonitis.....	7	4.2
Acute Gangrenous Cholecystitis with localized perforation.....	6	3.6
Total.....	160	100

purulent contents and verified by smear and culture; 7 patients, or 4.2 per cent, showed a perforation with generalized peritonitis; while 6 patients, or 3.6 per cent, showed acute gangrenous cholecystitis with perforation and abscess formation.

In 10 patients with acute cholecystitis, penicillin was administered intramuscularly every three hours up to the time of the immediate period before surgery in doses of from 30,000 to 100,000 units. In 8 of these patients the contents of the gallbladder failed to show any penicillin; in the other two patients the penicillin level of the gallbladder contents was shown to be .00329

and .002 units per cc., which is usually considered ineffective in combatting most of the pathogenic bacteria. Antibiotic therapy, however, is certainly indicated in an attempt to prevent or control the septic complications.

In 1936 a general policy was adopted for the treatment of patients with acute cholecystitis on this hospital service, and with some exceptions has been followed since. Patients seen during the first three days of the attack are operated upon unless there is some contraindication to surgery. Patients seen after that time are kept under observation and in the event that progression is noted in any of the findings, namely, temperature, pulse, pain, tenderness, rigidity, white blood cell count, polymorphonuclear or nonfilament count, the patient is operated upon after proper preparation. If during this period the patient's findings all improve, the inflammation is allowed to subside and the patient is operated on during an interval. If during the period of regression the patient suddenly has a recurrence of acute cholecystitis, operation is done immediately. We prefer to wait after the 11th day and as long as four or five weeks before operating upon a patient with subsiding acute cholecystitis. As will be noted, the increased mortality rate for surgery undertaken on the 4th to 8th day was therefore due mainly to the fact that the inflammatory process was progressing or that perforation had already taken place.

Cholecystostomy is usually done through a short paracostal incision under local anesthesia, the gallbladder being opened and an attempt made to remove the obstructing stones, since 93 per cent of the patients with acute cholecystitis have gallstones. Cholecystectomy is often accomplished in patients who have a small abscess between the gallbladder and the liver or around the neck of the gallbladder, but cholecystostomy is indicated in the presence of large abscesses. Cholecystostomy may also be done in the severely ill patient with acute cholecystitis and jaundice from acute hepatitis, or acute cholangitis associated with a common duct stone, the complete operation being deferred to a later period. In patients with associated acute pancreatitis and cholecystitis, cholecystostomy may be the procedure of choice.

#### SUMMARY

1. The presence of a positive bacterial culture in patients with acute cholecystitis does not necessarily mean that the organisms are pathogenic in the etiology of this disease.
2. The lower incidence of positive culture during the first three days of acute cholecystitis is associated with a low mortality rate when surgery is carried out during that period.
3. The highest mortality rate occurs with operation between the 4th and

8th days when the incidence of positive bacterial cultures and perforation is at its highest.

4. The mortality rate and the incidence of positive culture drop between the 11th and 35th days.

5. At least 53.3 per cent of the complications of cholecystitis are due to bacterial infection which may be avoided by earlier surgery and by proper use of antibiotic therapy.

6. This study suggests that the etiology of acute cholecystitis must be based on a mechanical circulatory or chemical origin and that bacterial infection plays a secondary role which accounts for the majority of the morbidity of complications and mortality.

The bacteriological studies were carried out under the supervision of Drs. Raymond J. Reitzel and Arthur Haim.

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# EFFECT OF INSULIN HYPOGLYCEMIA ON GASTRIC SECRETION IN DUODENAL ULCER AND CONTROLS\*

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## INTRODUCTION

Subcutaneous, intramuscular, or intravenous injection of insulin provokes a secretion of acid gastric juice in man and dog. This secretion can be prevented or erased by the intravenous or peroral administration of glucose, or, by the simultaneous administration of adrenalin<sup>10</sup>. The secretion takes place only after the blood sugar falls to a hypoglycemic level. The level to which the blood sugar falls after the intravenous injection of 15–20 units varies from 25 to 65 mg.%. Though it is claimed that a gastric secretory response may be obtained at a higher level it is safer to judge the absence or presence of the response only after a fall at least to 50 mg.% has been obtained<sup>9</sup>. The situation is not fundamentally changed in the diabetic, because there also a fall to hypoglycemic levels after an adequate dose of insulin causes the expected gastric secretion<sup>12</sup>. Clearcut proof that insulin acts via hypoglycemia and that this hypoglycemia acts through central vagus stimulation was furnished by the following facts. In dogs, atropine prevents the gastric secretory response to insulin<sup>2</sup>. This was found also in man, though rather large amounts of atropine (1.5 mg) were necessary<sup>4</sup>.

Section of the vagus nerves completely abolishes the secretory response to insulin, although it does not interfere with the action of histamine on the stomach<sup>13,11</sup>. It is thus seen that insulin hypoglycemia acts exclusively on the vagus nucleus and has no peripheral action, that means that it acts neither directly on the gastric secretory cells nor on intragastric nerve plexuses nor on ganglion cells nor on the peripheral circulatory mechanisms which may be of importance in gastric secretion. The final proof that it is the vagus center which is thus responsible for the insulin action on gastric secretion was furnished in an experiment by La Barre and Cespedes<sup>11</sup>, who were able to stimulate gastric secretion in a dog whose head remained connected with the trunk only by the vagus nerves, and whose head received blood by cross circulation from a dog made hypoglycemic with insulin.

The fact that insulin causes gastric secretion only through the vagus nucleus has led to the use of insulin hypoglycemia as a test for the completeness of severance of the vagal innervation of the human stomach (Hollander,<sup>5</sup>). It may be inferred from the known facts that a positive postoperative secretory gastric acid response to insulin hypoglycemia, whether in dog or in man, denotes that the procedures in-

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tended to interrupt the entire vagal innervation of the stomach have not been performed successfully.

The gastric juice secreted in response to insulin hypoglycemia reaches a free and total acidity about equal to that of histamine juice. It contains more pepsin and apparently more mucus<sup>6,16</sup>. The composition of this juice therefore resembles strongly that of the typical vagal juice obtained by sham feeding. The highest rise in acidity in humans was found by Rohholm to occur 40-60 minutes after intravenous administration<sup>14</sup>. In our material, we found the high point usually 90-105 minutes after giving the insulin. Subcutaneous administration seems to give greater variations in the time and degree of the acidity response. Variations of the dosage of intravenously administered insulin showed that 5 units are rarely sufficient to lower the blood sugar to the critical level of 50 mg.%<sup>6</sup>, whereas 15 units give uniform results in this respect, except in isolated instances. The insulin test has thus far been used clinically chiefly to determine the completeness of vagotomy. In an extensive study by Ihre<sup>6</sup> it was employed in conjunction with histamine to test the vagal and chemical phases of gastric secretion during a single test procedure. The total volume of gastric secretion was collected by using the double Agren tube, which allows continuous, separate withdrawal of duodenal and gastric contents. Saliva was removed by constant suction from the mouth. 16 units of insulin were given intravenously one hour after an injection of histamine. It was found by Ihre that this dose of insulin was sufficient to bring about marked stimulation of the vagus in all cases. The most marked hypoglycemic levels reached were between 24 mg.% and 67 mg.%. It was found that an increase of the amount of insulin to 20 units did not produce any stronger effect. Ihre also found that the gastric secretory response coincides with, or immediately follows the lowest point of hypoglycemia. Hollander, however, found that the rise in the secretory curve starts about the time the blood sugar curve falls to below 50 mg.%, not at or after the minimum. It furthermore was found that pepsin secretion was markedly stimulated by the insulin hypoglycemia and that it reached much higher values than after histamine; it was assumed that histamine had mainly a washing out effect on the peptic cells, whereas stimulation of the vagus led to a true increase in secretion of the peptic cells. In the pathological material studied by Ihre, cases with duodenal ulcer showed hypersecretion, i.e. an increased volume of secretion after histamine and insulin.

#### CLINICAL APPLICATION

Although the ultimate cause of peptic ulcer is unknown, all authorities agree that the mechanism of its production is connected with the action of free hydrochloric acid and pepsin on a susceptible mucosa. It therefore is of the greatest importance to study closely this "acid" factor. Previous studies by one of the authors (Winkelstein) seem to have demonstrated that the chemical (hormonal) phase as studied with bouillon and histamine is not disturbed in peptic ulcer. However, when the response to sham feeding (chewing of an orange) and the night-secretion were studied, he found that these were mark-

edly increased in patients with duodenal ulcer<sup>17</sup>. It is agreed by physiologists<sup>1</sup> that the response to sham feeding and the night-secretion are both produced through vagal mechanisms. In view of the strong probability that peptic ulcer is ultimately a psychosomatic disease<sup>19</sup> and in view of studies which indicate that the persistence of free acid after subtotal gastrectomy is due to vagus nerve influence<sup>17</sup>, it seems increasingly important to study the cephalic or vagus phase of gastric secretion in ulcer. This would help to elucidate the

TABLE I  
*Control Cases Given 15 Units Insulin Intravenously*

PATIENT NO.	FREE ACIDITY IN CLINICAL UNITS			BLOODSUGAR MG %	
	Fasting	Maximum	Rise from fasting level	Fasting	35 minutes
1	0	52	52	115	30
2	0	54	54	95	40
3	0	30	30	50	30
4	0	50	50		30
5	0	60	60		56
6	0	36	36		20
7	0	52	52		40
8	0	30	30		50
9	0	16	16		35
10	0	36	36		25
11	0	56	56		60
12	8	58	50		50
13	0	32	32		15
14	0	35	35		23
15	0	40	40		15
16	0	60	60		25
17	0	26	26		26
18	0	54	54		23

Average rise: 43

Average bloodsugar at 35 min.: 32 mg %

*Comment:* In 18 control cases the highest free acidity values after the hypoglycemia averaged 43 units. If we consider the fasting level the average rise was also 43 units. The average bloodsugar 35 minutes after the intravenous insulin administration was 32 mg %.

problem of the pathologic physiology of gastric secretion in the ulcer disease more fully.

Because of these considerations it was decided to study the effects of insulin given in varying doses and through different routes (subcutaneous and intra-venous) on gastric secretion in normals and in patients with duodenal ulcer.

#### MATERIAL

Patients in the Gastrointestinal Clinic with chronic uncomplicated duodenal ulcer were utilized for this study. The normals were chosen from a group with

TABLE II  
*Duodenal Ulcer Cases Given 15 Units Insulin Intravenously*

PATIENT NO.	FREE ACIDITY IN CLINICAL UNITS			BLOODSUGAR MG %	
	Fasting	Maximum	Rise from fasting level	Fasting	35 minutes
1	10	68	58		35
2	26	104	78		15
3	16	110	94		30
4	0	86	86		40
5	48	106	58		25
6	0	86	86		30
7	0	62	62		20
8	10	70	60	90	40
9	20	90	70	90	20
10	44	72	28	70	30
11	0	100	100	110	65
12	20	84	64	110	35
13	0	70	70	75	15
14	0	122	122	75	30
15	30	146	116	75	30
16	0	70	70	60	50
17	18	102	84	80	20
18	0	90	90	90	40
19	30	98	68	85	23
20	22	88	66	80	30
21	24	118	94	70	20

Average rise: 77 units

Average bloodsugar at 35 min.: 31 mg %

*Comment:* In 21 patients with duodenal ulcers the highest free acidity values after the hypoglycemia averaged 92 units, disregarding the fasting level. If we consider the fasting level, the average rise was 77 units. The average bloodsugar at 35 minutes after the intravenous insulin administration was 31 mg %.

TABLE III  
*Patients with Gall Bladder Disease Given 15 Units Insulin Intravenously*

PATIENT NO.	DIAGNOSIS	FREE ACIDITY			BLOODSUGAR MG %	
		Fasting	Maximum	Rise	Fasting	35 minutes
1	Postcholecystectomy syndrome	0	88	88		35
2	Same	16	84	68	110	50
3	Same	0	88	88	90	25
4	Same	0	70	70	60	20
5	Gall stones	14	90	76		35
6	Cholecystitis	20	88	68	80	50
7	Biliary dyskinesia	0	80	80		30

Free Acidity, Average rise: 77 units

Bloodsugar: Average rise at 35 minutes: 35 mg %

*Comment:* In 7 cases of various types of gall bladder disease (including 4 cases of the postcholecystectomy syndrome) the acidity response to the hypoglycemia produced by 15 units of insulin intravenously was as high as in the duodenal ulcer cases.

TABLE IV  
*Controls and Ulcers Given 15 Units Insulin Intravenously (2 separate tests)*  
*Constancy of Response*

PATIENT NO.	DATE	DIAGNOSIS	FASTING	MAXIMUM	RISE FROM FASTING LEVEL	BLOODSUGAR MG %
						Fasting 35 min.
1	6-13-47	Control	0	28	28	30
1	6-20-47		0	40	40	15
2	6-4-47	Control	0	35	35	25
2	6-11-47		0	35	35	23
3	6-2-47	Control	0	60	60	15
3	6-13-47		0	58	58	20
4	6-9-47	Control	16	60	44	15
4	6-23-47		0	60	60	25
5	6-9-47	Control	0	24	24	20
5	6-27-47		0	32	32	15
6	6-16-47	Control	12	56	44	25
6	6-27-47		0	54	54	23
7	6-9-47	Control	0	28	28	20
7	6-27-47		0	30	30	20
8	3-15-48	Peptic ulcer	6	102	96	20
8	3-22-48		6	92	86	30
9	6-9-47	Peptic ulcer	12	90	78	50
9	6-30-47		20	88	68	15

*Comment:* Repeated insulin tests meals (controls and ulcers) show practically the same type of response (*in the same patients*).

TABLE V  
*Achlorhydria Cases Given 15 Units Insulin Intravenously*

PATIENT NO.	DIAGNOSIS	BLOODSUGAR MG % (35 MIN. AFTER INSULIN)	RESPONSE (FREE HCl)
1	Achlorhydria (histamine)	35	0
2	Achlorhydria "	35	0
3	Achlorhydria "	40	0

*Comment:* In 3 cases of histamine refractory achlorhydria, there was no rise in free acidity after 15 units of insulin intravenously.

vague or transient digestive symptoms with negative X-ray findings. They were instructed to eat a light supper the previous night and to present them-

TABLE VI  
*Controls Given 5 Units Insulin Intravenously*

PATIENT NO.	FREE ACIDITY			BLOODSUGAR MG %	
	Fasting	Maximum	Rise from fasting level	Fasting	35 minutes
1	0	54	54	90	60
2	0	64	64	80	55
3	0	54	54	80	25
4	0	52	52	105	80
5	0	40	40	100	60
6	0	44	44	90	60
7	0	18	18	90	45
8	16	74	58	80	55
9	0	30	30	75	65
10	0	14	14	85	50
11	0	38	38	80	30
12	20	42	22	105	50
13	8	92	84	70	34
14	0	25	25	80	40

Average rise: 43

Average 35 minutes: 50 mg %

*Comment:* In 14 controls, the average acidity rise after 5 units of insulin given intravenously was 43 clinical units. The average of the bloodsugar after the insulin in 14 cases was 50 mg %.

TABLE VII  
*Duodenal Ulcer Cases Given 5 Units Insulin Intravenously*

PATIENT NO.	FREE ACIDITY			BLOODSUGAR MG %	
	Fasting	Maximum	Rise from fasting level	Fasting	35 minutes
1	0	54	54		
2	0	30	30		
3	22	58	36		
4	0	90	90		
5	18	80	62	80	65
6	18	70	52	80	60
7	58	80	22	130	55
8	0	64	64	90	45

Average rise: 51

Average 35 minutes: 56

*Comment:* Despite a fall in bloodsugar to only 56 mg %, there was an average rise of 51 units in the free acidity in 8 duodenal ulcer cases. This is 10 units (20%) higher than the control group's average rise of 41 units after a bloodsugar fall to 50 mg %. Whether this figure is significant is a question for further study.

selves in a fasting state at 9 a.m. the following morning. A 14 French Levin tube was passed into the stomach and the fasting contents aspirated for 15 minutes and then every 15 minutes after the insulin injection for a period of

TABLE VIII

*Subcutaneous and Intravenous Insulin Administration compared in Duodenal Ulcers and Controls*

PATIENT NO.	DIAGNOSIS		
1	Duodenal ulcer	Subc. 20 units Bloodsugar: 65-60 mg % rise: 20-34 (14) free HCl	i.v. 15 units Bloodsugar: 40 mg % rise: 10-86 (76)
2	Duodenal ulcer	Subc. 20 units Bloodsugar: 40 mg % rise: 52-98 (46) free HCl	i.v. 15 units Bloodsugar: 30 mg % rise: 0-100 (100)
3	Ess. Hypertension No G.I. series done	Subc. 20 units Bloodsugar: 40 mg % rise: 4-38 (34) free HCl	i.v. 15 units Bloodsugar: 75 mg % rise: 0-102 (102)
4	Duodenal ulcer	Subc. 20 units Bloodsugar: 50 mg % rise: 0-62 (62)	i.v. 15 units Bloodsugar: 75 mg % rise: 0-90 (90)
5	Duodenal ulcer	Subc. 20 units Bloodsugar: 100 mg % fall: 36-0	i.v. 15 units Bloodsugar: 70-35 mg % rise: 26-80 (54)
6	Hiatus hernia Diverticulitis of colon	Subc. 20 units Bloodsugar: 80 mg % fall: 26-18 (8)	i.v. 15 units Bloodsugar: 70-35 mg % rise: 8-58 (50)
7	Hyperacidity No d.u. Bronchiectasis	Subc. 20 units Bloodsugar: 80 mg % fall: 50-36 (14)	i.v. 15 units Bloodsugar: 25 mg % rise: 38-102 (64)
8	Functional	Subc. 20 units Bloodsugar: 30 mg % rise: 0-18 (18)	i.v. 15 units Bloodsugar: 25 mg % rise: 0-36 (36)
9	Colitis	Subc. 20 units Bloodsugar: 40 mg % rise: 14-26 (12)	i.v. 15 units Bloodsugar: 60 mg % rise: 0-56 (56)

*Comment:* Whereas all nine patients showed a significant rise of acidity after 15 units of insulin given intravenously, only 3 of these patients gave a significant response after subcutaneous insulin administration even though the dose was increased to 20 units.

This route of administration should therefore not be used to determine the gastric secretory response to insulin. Apparently the rate and degree in the fall of the blood sugar fluctuates too widely for constant results.

TABLE IX  
*Summary of Results*

	AVERAGE MAXIMUM RISE FREE HCl	AVERAGE BLOODSUGAR 35 MIN.
15 Units Insulin Intravenously		
Control cases.....	units 43	mg % 32
Duodenal ulcer.....	77	31
Gall bladder disease.....	73	39
Achlorhydria (histamine).....	0	37
5 Units Insulin Intravenously		
Control cases.....	41	50
Duodenal ulcer.....	51	56

2 hours. Insulin was administered intravenously. While it was realized that a fasting blood sugar and several specimens after the insulin would perhaps yield more information, a determination while fasting and 35 minutes after the insulin seemed more practical in an outpatient department. We will present the results of our studies in the different groups of cases in the following tables. At the end of each table we will comment briefly on the data presented.

#### DISCUSSION

As already stated, it is a clearly established fact that insulin hypoglycemia stimulates the vagus nucleus. An analysis of the acidity values as presented in the accompanying tables, indicates that the vagus nucleus is hyperirritable in patients with duodenal ulcer as compared with normals. Even lesser drops in blood sugar (50—60 mg. %) evoke a higher acid response in ulcer patients than in normals.

In anticipation of a possible criticism not only were patients without ulcer studied as controls but ulcer patients and normals were given repeated tests (See Table IV.). In one patient 20 insulin tests were carried out adding various pharmacological agents and yet the curves were all practically identical.

This study seems to give further support to the rationale of vagotomy in the therapy of peptic ulcer, whether used as a prophylactic measure against post-operative recurrence after subtotal gastrectomy<sup>18</sup> or as a primary curative measure for duodenal ulcer (Dragstedt,<sup>3</sup>).

Another aspect of this problem which has interested us for many years is the possible relation of the sugar metabolism to gastric secretion and peptic ulcer. The rarity of the occurrence of peptic ulcer in patients with diabetes mellitus is notorious. The hyperglycemic level in diabetics may indeed exert a sedative effect on the vagus nucleus. On the other hand there exists the possibility that the "hunger" pains and the night pains of ulcer patients may be of hypoglycemic origin, or, at least may result from sudden drops in blood sugar levels even if these are not great. A pancreatic factor (hyperinsulinism) or even an anterior pituitary factor may accordingly be of importance via blood sugar variations in the pathologic physiology of gastric secretion in peptic ulcer.

Parenthetically, the rather marked acidity response in the gallbladder cases is of interest. If these results are constantly found in a larger group, one may be able to judge more accurately the role of excessive vagal activity in gall bladder diseases, more specially in the post cholecystectomy syndrome and in biliary dyskinesia. It would seem worthwhile to study the possible beneficial effect of vagotomy in these two conditions.

From the therapeutic point of view it seems indicated to evaluate a variety of agents which could possibly act in a sedative fashion on the vagus nucleus.

One may mention the acid-base equilibrium; the blood sugar level; the blood calcium; psychotherapy; and the effect of central sedatives. A systematic study of the effects of a variety of such agents on the gastric acidity response to insulin hypoglycemia might lead to new approaches in the therapeutic management of ulcer. To date, men with conventional therapies have attempted to obtain an antivagal effect by using chiefly the atropine group of drugs which act peripherally. We think that an attack on the higher center, i.e. the dorsal vagus nucleus, seems more logical.

#### SUMMARY AND CONCLUSIONS

1. Previous studies have established that insulin hypoglycemia stimulates the dorsal vagus nucleus.
2. This vagal stimulation results in increased secretion of hydrochloric acid in the stomach.
3. Theoretic considerations suggest that the vagus nerves play an important role in the genesis of peptic ulcer.
4. Our studies were directed to determine the role played by the dorsal vagus nucleus in the gastric secretory disturbances of duodenal ulcer.
5. We have found that 15 units of insulin given intravenously evokes a markedly higher acid response in duodenal ulcer patients than in normals.
6. Smaller doses (5 units intravenously) act likewise but give less marked responses.
7. Subcutaneous administration of insulin was found to be unreliable as a test for vagal gastric acid secretion.
8. Insulin hypoglycemia was found to give exaggerated acidity responses also in patients with gall bladder disease.
9. The results of these studies favor the use of vagotomy in the surgical therapy of duodenal ulcer.
10. The relation of the sugar metabolism to the vagus nerve function and to peptic ulcer is also discussed.
11. These studies suggest that it is probably of fundamental importance to control or allay the hyperirritability of the dorsal vagus nucleus in the therapy of peptic ulcer.

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## DISCUSSION

DR. LESTER DRAGSTEDT (Chicago, Ill.): This paper by Drs. Winkelstein and Hess is an interesting and important contribution to the study of the pathogenesis of ulcer. It confirms in a striking way the previous researches of Welin and Frisk at St. Erik's Hospital in Stockholm, Sweden. These investigators reported that patients with duodenal ulcer secreted from two to three times as much gastric juice in response to a standard dose of insulin given intravenously as did normal individuals. Similar observations were subsequently made by Bengt Ihre, also in Sweden. In our Clinic, we have also observed a similar increased response on the part of patients with duodenal ulcer to a standard dose of insulin as compared with normal individuals. In a study recently conducted with my associate, Dr. Harry Oberhelman, Jr., we have found that duodenal ulcer patients yield a similarly exaggerated gastric secretory response to a standard dose of histamine. Thus, in 18 normal males, an average of 13.2 milliequivalents of hydrochloric acid were secreted in 60 minutes after the subcutaneous injection of 1 milligram of histamine. In contrast to this, a group of 15 males with peptic ulcer put out 17.3 milliequivalents, and a second group of 18 males with duodenal ulcer put out 27 milliequivalents of hydrochloric acid, or almost twice as much as the normal individual in response to the same dose of histamine. It is very significant, I think, that not only does the patient with duodenal ulcer secrete abnormally large amounts of gastric juice when there is no physiological stimulus to

the stomach, but that he also secretes an excessive amount in response to the usual stimuli for gastric secretion.

Complete division of the vagus nerves to the stomach reduces very markedly the gastric secretory response to a standard dose of histamine as compared with the pre-operative level. Thus, the first group of ulcer patients secreted 17.3 milliequivalents of hydrochloric acid in response to the subcutaneous injection of 1 milligram of histamine phosphate before vagotomy, and after vagotomy the secretion fell to an average of 6.1 milliequivalents. In the second group of ulcer patients, an average of 27.0 milliequivalents of hydrochloric acid was put out before vagotomy and only 5.5 milliequivalents after the operation. A similar effect was found in total pouch dogs with vagus innervation to the pouch intact. This decreased secretory response of the stomach to histamine after vagotomy, which we have customarily thought acts peripherally on the gastric glands, does not necessarily mean that the action is in part on the vagus centers. It is conceivable that in some way the sensitivity of the glandular apparatus is reduced by vagotomy so that a humoral stimulus which acts peripherally now gives a smaller response than it did before.

DR. ASHER WINKELSTEIN (New York, N. Y.): In reply to Dr. Dragstedt's remarks about histamine, it may be stated that his studies show clearly that the acidity concentration is the same in normals as it is in the ulcer patients. He is demonstrating merely a difference in the volumetric output.

We studied this problem many years ago and found the acid concentration, after histamine, was the same in normals and in ulcer patients. One of the main points in our paper this morning, and, what we have emphasized all along, is that the increased acidity in the ulcer patients is in the vagal phase and not in the chemical phase.

I should like to add a few points to Dr. Hess' presentation. We have done repeated tests in the same patients and found the curves practically constant in the same patients. This fixed character of the response to insulin hypoglycemia is striking. Perhaps it is constitutional. We have tried many pharmacological agents in an effort to reduce the vagus nucleus hyperirritability, without success.

In one patient, we used successively seventeen different drugs combined with insulin hypoglycemia and were unable to alter the curve.

The relation of the sugar metabolism seems important. As you know, ulcer is very rare in true diabetics. Is this due to a sedative action of the hypoglycemia? Are the hunger pains and night pains in ulcer associated with hypoglycemia? Does vagotomy act by lessening hypoglycemia? These questions require further study.

The main point of our paper is that the attack on the vagus should be central rather than peripheral. Using insulin hypoglycemia as a test, we could study a variety of agents which might attack the central vagus nucleus. Such agents include psychotherapy, shock therapy, the effect of high protein diet, the acid base shifts, central sedatives, and many others. These should be studied in the hope that some good agents may be found which will allay the hyper-irritability of the central vagus nucleus in peptic ulcer.

## ACUTE ESOPHAGEAL ULCERATION ASSOCIATED WITH INTRANUCLEAR INCLUSION BODIES

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In 1943 Pearce and Dagradi reported the finding of 4 cases of acute ulceration of the esophagus with intra-nuclear inclusion bodies in the epithelium bordering on the ulcers. In 2 of these cases it was stated that the ulcers were rounded as contrasted with the majority of acute esophageal ulcers which are oblong and lying in the longitudinal axis of the esophagus.

Since inclusion bodies of the type found by Pearce and Dagradi<sup>1</sup> are good presumptive evidence of virus infection and in 2 of their cases the cause of death was ulcerative colitis it was suggested that the virus that was associated with the esophageal ulceration might have caused the colitis although no inclusion bodies were found in the colonic ulcers. Likewise Alvarez<sup>2</sup>, calling attention to the findings of Pearce and Dagradi<sup>1</sup> recommended the search for little ulcers with inclusion bodies in other parts of the digestive tract during autopsies on patients who died from regional enteritis or ulcerative colitis.

Since demonstrating for the first time the association of an ulcer of the esophagus with nuclear inclusion bodies—in this case the so-called protozoan-like bodies<sup>3</sup>—a search for inclusion bodies was made in all cases of acute esophageal ulceration in our autopsy material. Only recently we succeeded in finding nuclear inclusion bodies in a second case. This time the inclusion bodies were of a different type and the gross and microscopical findings in the esophagus almost identical with those described by Pearce and Dagradi<sup>1</sup>.

### CASE REPORT

A 49 year old colored woman entered the hospital with a diagnosis of pulmonary tuberculosis and died a few weeks after admission.

At autopsy there was pulmonary tuberculosis with caseous pneumonia, laryngeal tuberculosis, tuberculosis of the left kidney and small caseous foci in the liver and spleen. There was acute, pseudo-membranous inflammation of the terminal 30 cm. of the ileum.

In the lower third of the esophagus there were a number of rounded shallow ulcers of a diameter not more than 2 mm. and covered with yellowish exudate.

### MICROSCOPIC EXAMINATION

The esophageal ulcers did not reach deeper than the more superficial part of the mucous membrane which was loosely infiltrated by polymorphonuclear leukocytes, a few lymphocytes and plasmacells. The venules of the mucous



FIG. 1

membrane contained numerous leukocytes. The ulcers were covered by a layer of fibrin containing many more or less degenerated leukocytes. No bacteria could be demonstrated inside this fibrinous layer.

The epithelial cells at the margins of the ulcers often stained more palely



FIG. 2

than those farther distant. This zone of pale staining cells varied in width. Many cells were distinctly swollen. The nuclei of the swollen cells were large and contained distinct inclusion bodies of varying size and shape (Fig. 1). Mostly they were round or oval but sometimes of an irregular form. They

stained red with azophloxin and dark red with Masson's trichrome. In the inclusion-bearing nuclei there was margination of the chromatin and the inclusion bodies were surrounded by a clear halo. Sometimes the entire nucleus was filled by a more purplish staining body. In several places there was a peculiar clumping of the inclusion-bearing nuclei, 5 to 8 nuclei lying close together (Fig. 2).

Other inclusion-bearing cells were almost of normal size.<sup>1</sup> They were lying in the deeper layers of the epithelium.

The ileum showed an acute, pseudomembranous inflammation without specific features. No inclusion bodies were found there. There were enormous numbers of bacteria in the necrotic layer.

#### DISCUSSION

It is evident from the description and the photomicrographs that the lesions found in the esophagus were almost identical with those described by Pearce and Dagradi<sup>1</sup>. Especially typical was the form of the ulcers, which in our case and at least in 2 cases of Pearce and Dagradi were rounded. It is also of interest that the inclusion bodies were found in the deepest layers of the epithelium, which renders the conception that the inclusion bodies are mere artefacts caused by the degeneration of the superficial cell layers improbable. They also showed resemblance to the inclusion bodies caused by virus superinfection of the rabbit papilloma strain, and of epidermoid carcinoma derived from virus papilloma<sup>4</sup>.

In the ileum there was an acute pseudomembranous inflammation and no inclusion bodies were found there. Therefore it is not probable that the inflammatory processes in the ileum and in the esophagus were caused by the same agent, so that our case does not bring the problem of the eventual viral etiology of chronic ulcerative colitis and regional enteritis nearer to its solution. It stresses however the necessity of the microscopic examination of seemingly unimportant lesions of the gastro-intestinal tract in routine autopsy material.

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## THE EFFECT OF DEMEROL UPON THE SPHINCTER OF ODDI IN MAN\*

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Knowledge of the effect of various drugs upon the sphincter of Oddi is obvious clinical importance. Previous studies have been carried out to investigate the action of many of the common drugs<sup>1,2</sup>. The present report deals with a study of the effect of demerol hydrochloride (ethyl-1-methyl-4-phenylpiperidine-4-carboxylate, or isonipecaine) upon the sphincter mechanism of the common bile duct.

### METHOD

Patients who previously had undergone cholecystectomy, choledochotomy and intubation of the common bile duct served as subjects for these studies. As a preliminary procedure the anatomic status of the bile ducts was demonstrated to be normal by cholangiographic examination.

It has been our practice to measure the sphincter resistance postoperatively in every patient with a choledochostomy tube<sup>3</sup>. No such tube has been removed until the sphincter resistance has been normal. This procedure has permitted evaluation of the action of various drugs upon the sphincter.

The apparatus, which was sterilized in the autoclave, consisted of an infusion flask connected by a rubber tube to the choledochostomy tube. A Murphy drip bulb was included in the system so that observations of flow could be made. The fluid in the system was sterile physiological salt solution.

The sphincter resistance was measured by a method previously described. By elevating or lowering the infusion flask, the pressure within the duct system could be altered, and it could be read directly on a centimeter scale which was set so that the zero point was at the estimated level of the common bile duct. The column of saline solution was adjusted to the level at which it was just supported without allowing any flow, and this pressure was recorded as *sphincter resistance*. Normally the sphincter can withstand pressures between 12 and 23 centimeters of water, and the sphincter resistance is more often around 12 to 15 centimeters.

Measurements of sphincter resistance were made successively at intervals of one minute. After fifteen to thirty minutes of preliminary measurement

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## THE EFFECTS OF CERTAIN SO-CALLED ANTISPASMODICS ON INTESTINAL MOTILITY\*

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The motor functioning of the human intestine is a complex form of activity made up of three basic components: tone, motility and the intersegmental relationships. By tone we infer the resistance offered by the intestinal musculature to any distending force. Under "motility" we include those forms of rhythmic contraction and peristalsis which produce configurations of types I, II and III on tracings obtained from the bowel.† The intersegmental relationships apply to the adjacent functional segments that comprise the intestinal tract, and include both intersegmental coordination and incoordination. Intersegmental incoordination is the physiologic blocking mechanism which prevents the too rapid aboral transport of intestinal contents; it connotes a functional motor independence between two adjacent segments. Intersegmental coordination is the phenomenon whereby the motilities of two adjacent functional segments become so integrated that the two segments act as a single motor unit; without this mechanism, transport of fecal material, especially solid feces, is virtually impossible.

Abnormalities in motor function may involve any of these three basic components, separately or in various combinations. Such disturbances occur in association with various organic and functional states and give rise to a variety of symptoms, including constipation, diarrhea, bloating and cramping. Although spasm may exist in the intestinal tract, it is highly probable that the majority of symptoms interpreted as being due to spasm are in reality the result of a dyssynergia between adjacent functional segments of the bowel.

In clinical practice, the treatment of disturbances of motor function is empirical and usually consists of the administration of so-called antispasmodic drugs, which are said to inhibit the motility and depress the tone of the gastro-

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† Templeton, R. D. and Lawson, Hampden: Am. J. Physiol., 96: 667, 1931; also Adler, H. F., Atkinson, A. J. and Ivy, A. C.: Am. J. Digest. Dis. 8: 197, 1941.

intestinal tract. In most instances, these drugs are given by mouth. The treatment of motor abnormalities by these means seems far from satisfactory.

In general, the basis for the prescription of antispasmodic drugs is on routine pharmacologic testing of isolated intestinal strips, the injection of the pharmaceutical preparation into animals following stimulation of the intestine, and clinical investigation, whereby the clinician and occasionally the patient attempt to evaluate the patient's response to the drug. A few definitive studies have been carried out employing the human subject in which intestinal motility has been recorded before and after an injection of the drug. Occasionally in the course of such an investigation, the drug has been given orally. It is surprising, however, that a search of the literature reveals no comparative studies on the effects of drugs administered by mouth on the intestinal motility of human beings. Yet this is the usual manner in which such preparations are prescribed by the physician.

It has frequently been pointed out that the effects of pharmaceutical preparations employed in the treatment of human ills should be studied on the human being. It is obvious that only by ascertaining the effects of a drug on the human being after it has been administered by the usual route can we be certain of its action.

#### PURPOSE OF STUDY

We have undertaken a survey of several so-called antispasmodic drugs in an effort to determine whether these drugs, when given in the recommended therapeutic doses and by the oral route, alter either intestinal tone or motility. The preparations included in this study are: amethone, octin, NU-72-4D, pavatrine, syntropan, novatrin, trasentine, phenobarbital, ephedrine and atropine.

We wish to express our appreciation to the Abbott Laboratories for providing supplies of amethone, to the Bilhuber-Knoll Corporation for furnishing octin, to Hoffmann-LaRoche, Incorporated, for NU-72-4D and syntropan, and to G. D. Searle & Company for providing pavatrine.

#### HISTORICAL DATA

A review of current opinions concerning end results of experiments with these drugs would seem to be in order. For a more detailed review of the literature see thesis by one of us (E. L. P.).<sup>1</sup>

Atropine is an organic ester of tropic acid and tropine. Atropine is racemic and is composed of equal parts of d-hyoscyamine and l-hyoscyamine.<sup>2</sup> It is generally accepted that atropine, at least experimentally, is capable of inhibiting the tone and motility of the intestinal tract. Atropine is considered to act directly on the surface of the effector cell either to prevent attachment of acetylcholine or to prevent its response to acetylcholine attachment.<sup>2</sup> There is no interference with the local or the intracellular release of acetylcholine; thus parasympathetic stimulation continues to excite the intestine after atropinization.<sup>3</sup> Although certain investigators<sup>4,5</sup> have stated that only abnormally violent contractions are arrested by atropine, there is ample evidence that the action of the unstimulated human intestinal tract is inhibited by the drug both after parenteral<sup>4-7</sup> and oral<sup>8</sup> administration.

Pavatrine is  $\beta$ -diethylaminoethyl fluorine-9-carboxylate hydrochloride. This preparation has been found to inhibit tone and motility of the isolated intestine and to counteract neurotropic and musculotropic spasmogenic agents under experimental conditions.<sup>10</sup> Pavatrine is one-twentieth as active as atropine in reducing hypermotility in the human stomach induced by insulin.<sup>11</sup>

Amethone is 3-( $\beta$ -diethylaminoethyl)-3-phenyl-2-benzfuranone hydrochloride. Experimentally amethone inhibits the action of unstimulated intestinal strip and relaxes spasm induced by barium chloride, acetylcholine and arecoline.<sup>12</sup> It has been observed to produce inhibition in the distal portion of the colon of man within thirty minutes of its oral administration and to maintain this inhibition for as long as forty minutes.<sup>13</sup>

Phenobarbital is phenylethyl barbituric acid. It is classified as a long-acting barbiturate.<sup>2</sup> It has been observed to inhibit both the tone and motility of the unstimulated intestine of the dog after its injection.<sup>14</sup> It has been reported, however, that barbiturates may actually increase intestinal tone and motility in the dog.<sup>15</sup> Another barbiturate, pentobarbital sodium, has been found ineffective in inhibiting the functioning of the lower part of the bowel of human beings.<sup>16</sup>

Trasentine is diphenyl acetyl diethylaminoethanol hydrochloride. Experimentally trasentine relieves spasm in the intestinal strip induced by acetylcholine and barium chloride.<sup>16</sup> The preparation is said to have a selective type of action which is primarily effective on the gastro-intestinal tract and the uterus.<sup>17</sup> Its intravenous injection into human beings inhibited the action of the unstimulated intestinal tract.<sup>8</sup> On intramuscular or oral administration, it has inhibited the action of the unstimulated intestinal tract in 14 per cent of instances.<sup>18</sup> Intersegmental coordination is said to be improved by the drug.<sup>18</sup>

Syntropan is the phosphoric acid salt of the *dl*-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol. It has a musculotropic and neurotropic action, with an especial affinity for the smooth muscle of the gastro-intestinal tract and the uterus.<sup>19</sup> Syntropan has virtually no effect on the unstimulated intestinal tract of the dog; its injection after stimulation with acetylcholine causes inhibition of tone and motility for only ten minutes.<sup>20</sup> Its intravenous injection into the human being has been found to inhibit tone and motility of the unstimulated intestinal tract.<sup>8</sup> Syntropan has been found ineffective in the human being after intramuscular administration.<sup>18</sup>

Novatrin is homatropine methylbromide. It has been found to have an atropine-like effect on the isolated intestinal strip.<sup>21</sup> Its intravenous injection has inhibited the tone and motility of the unstimulated gastro-intestinal tract of dogs,<sup>22</sup> and the hypermotility of the human stomach induced by insulin.<sup>23</sup> The activity of the human gastro-intestinal tract has been inhibited for five to sixty minutes after the intramuscular injection of 2.5 mg. of novatrin.<sup>24</sup>

Octin is 2-methylaminoiso-octene. It acts on the isolated intestinal strip to depress slightly the tone and to cause rhythmic contractions to become somewhat less frequent.<sup>25</sup> It has been found inferior to atropine, trasentine and papaverine in relieving spasm due to acetylcholine in the isolated intestine of rabbits and inferior to papaverine and trasentine, but superior to atropine in relieving spasm induced by barium chloride.<sup>26</sup> Its intravenous injection into the dog diminishes tone and, to a lesser extent, rhythmic contractions; peristalsis is said to be inhibited.<sup>27</sup> Its intramuscular injection into human beings produced no demonstrable effects on intestinal tone or motility.<sup>18</sup> The lower saturated amines, of which octin is an example, are generally reported as increasing tone and motility in the intestine.<sup>28</sup>

NU-72-4D [2,6-di(*P*-methoxyphenethyl)-1-methylpiperidine hydrochloride] is a recently synthesized spasmolytic. According to information kindly provided by the manufacturers this drug is superior to papaverine, but inferior to atropine, in relaxing neurotropic spasm of the isolated intestinal strip, and is superior to both atropine and papaverine in combating myotropie spasm. Its neurotropic potency is apparently five to six times greater than its musculotropic effects. It is said to affect tone more than motility in the isolated intestine of rabbits.

Ephedrine is an alkaloid occurring in certain plants of the genus *Ephedra* and is identical with the Chinese drug, mahuang. It appears likely that it acts by antagonizing amine oxidase, the enzyme responsible for the destruction of epinephrine in the body.<sup>29</sup> Ephedrine has been observed to inhibit the tone and motility of the entire unstimulated gastro-intestinal tract of dogs<sup>30</sup> and human beings.<sup>31, 32</sup>

## METHOD AND PROCEDURE

An optical manometer-photokymographic technic with aid of tandem balloons of the type described elsewhere<sup>33</sup> was utilized (fig. 1).

The reactions of 24 patients from 15 to 73 years of age who consented to the tests were studied. Twenty-three had either ileal or colonic stomas or both. These had been made for a variety of conditions. One patient who had an irritable bowel was studied with the balloon system inserted high into the rectum. All patients were in good condition at the time of study with the exception of one, a girl 15 years old, who had a colonic stoma in the region of active ulcerative colitis. There were 16 males and 8 females in the group studied.

All medication was withheld for suitable periods preceding the tests. The patients were studied one hour after a light breakfast. Control records were obtained for sixty to ninety minutes on the

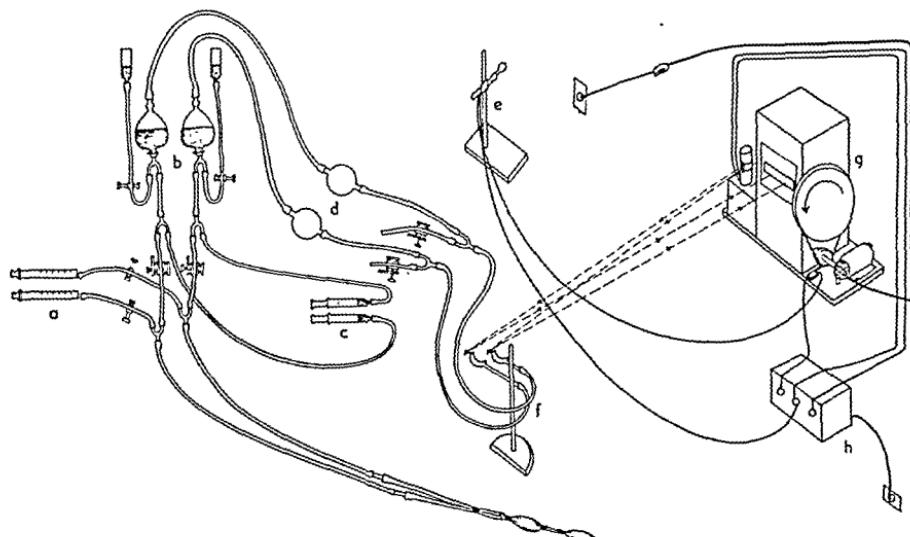


FIG. 1. Apparatus employed. The tandem balloon intubation device is shown in lower center portion of the illustration. *a*. Twenty cubic centimeter syringes used to inflate balloons. *b*. Water reservoir and side arms for filling reservoirs. *c*. Five cubic centimeter syringes for standardization of optical manometers. *d*. Adapters to damp out respiratory excursions. Side arms of safety valve just beyond adapters. *e*. Timer light. *f*. Optical manometers; dotted lines with arrows indicate beams of light leaving constant light source and being reflected from optical manometers into aperture of camera, *g*. *h*. Transformer.

day preceding the studies with the various drugs. On the day of the drug studies, control observations were made for twenty to forty minutes. The drug was given by mouth with a small cup (100 cc.) of water, and a continuous recording was made for sixty to ninety minutes afterward.

## RESULTS

In no instance was there any modification of the intersegmental relationships.

*Amethone.*—Amethone was administered ten times to 8 patients. Three patients had ileal stomas, 4 had colonic stomas and 1 patient had a stoma in the ileum as well as in the transverse colon. The drug was given orally in amounts of 50 or 100 mg. The size of the dose did not apparently determine the response. The intestinal motility of 3 patients was altered by amethone;

2 of these had been given 50 mg., the other, 100 mg. The latent period varied from nine to eighteen minutes. In all three cases, motility was abolished for an interval of eighteen to twenty-two minutes. Tonus was in no way affected.

One of these patients had a reaction to 50 mg. of amethone shortly after the drug had become effective. She became extremely apprehensive, restless and excited. Her pupils were widely dilated, her skin was flushed, and tachycardia of about 130 beats per minute was noted. She complained of vague sensations in her thorax and stated that her mouth was dry. After the motility had been abolished for twenty-two minutes, with the reaction still present, there was a sharp rise in tone. Tonus waves and respiratory excursions were superimposed on the recording, but no definite peristaltic contractions were noted (fig. 2). One and a half grains (0.1 gm.) of sodium phenobarbital was given hypodermically. Within ten minutes the tone had returned to normal levels, and the usual intestinal motility for this patient reappeared. The

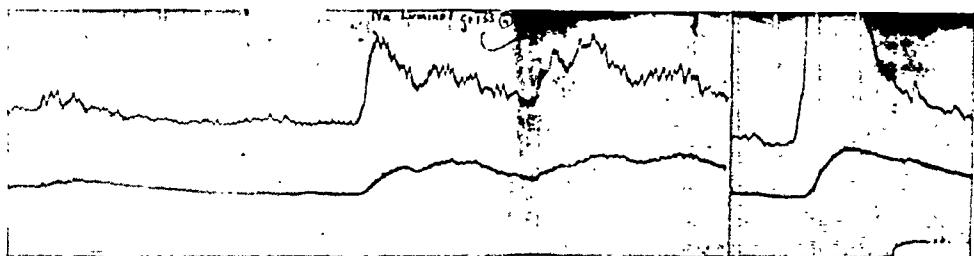


FIG. 2. Inhibition of motility in the descending colon (tandem tracing). Amethone, 100 mg. had been given thirty-one minutes earlier. Motility had been abolished for eleven minutes. A moderately severe reaction occurred. A sharp rise in tone which developed at the height of the reaction may be noted. Sodium phenobarbital 1½ grains (0.1 gm.) was given hypodermically as indicated. The tracing on right shows that ten minutes later tone decreased and the patient's usual motility reappeared.

subjective reaction was completely relieved within twenty minutes after the barbiturate was injected. A second of these patients had a delayed type of reaction, about three hours after 100 mg. of amethone had been given. The intestinal motility had been abolished for eighteen minutes, followed by complete recovery during the period of study. This reaction was mild, consisting of flushing of the face, mydriasis, photophobia, xerostomia, slight excitement and tachycardia. It subsided spontaneously in about forty minutes. A similar reaction was experienced by a third patient in whom the drug did not affect motility.

It is interesting to note that the depression of motility could not be repeated in 1 patient after stimulation of the colon by 0.5 mg. of prostigmine, nor could the amethone be potentiated in this instance by subsequent administration of 15 minimis of tincture of belladonna.

*Octin.*—Octin was given perorally in the amount of 120 mg. to 2 patients; one had an ileal stoma; the other was studied with the aid of the tandem system

of balloons inserted high into the rectum. In neither instance was tone or motility modified. No reactions to the drug were experienced.

*NU-72-4D.*—This preparation was administered orally in the amounts of 25 to 75 mg. five times to 4 patients. One patient had a colonic stoma and 3 had ileal stomas. The tone and motility of the intestinal tract were not altered by NU-72-4D in these dosages. One patient experienced a mild delayed reaction similar to that described after use of amethone.

*Pavatrine.*—The action of pavatrine alone was studied twelve times on 10 patients. Seven patient had colonic stomas and 3 had ileal stomas. An oral dose of 250 mg. of the pavatrine in tablet form was given ten times, and 125 mg. of pavatrine in rapidly dissolving capsules was given twice. The preparation altered neither intestinal tone nor motility in any instance. Reactions were not observed. One patient experienced mild excitement after pavatrine was given, but this could not definitely be ascribed to the drug. In a thirteenth study 250 mg. of pavatrine in tablet form and 32.5 mg. of phenobarbital were given to a patient who had an ileal stoma. Again the preparation had no effect on the intestine.

*Syntropan.*—Syntropan was administered orally in doses of 100 mg. to 1 patient who had an ileal stoma and to another who had a colonic stoma. In neither instance was any effect observed. Neither patient experienced a reaction to the preparation.

*Novatrin.*—This drug was given by mouth to 4 patients in amounts of 2.7 to 5.4 mg. One patient had an ileal stoma, and the other 3 had colonic stomas. In 3 cases, no effect was observed after administration of novatrin. In the fourth, who received 2.7 mg., a slight but definite increase in tonus was noted fifty-one minutes after the drug had been given. Motility per se was not altered. This increased tone had not subsided when the recording was discontinued twenty minutes later. No reactions to the preparation were experienced.

*Trasentine.*—Trasentine was administered orally in doses of 75 or 150 mg. to 5 patients. One patient had an ileal stoma and 4 had colonic stomas. In 4 cases, no effects were observed after administration of trasentine. In the fifth, the tone increased slightly but definitely thirty-five minutes after 75 mg. of the drug had been administered. Motility was not modified. The increased tone had not diminished when the recording was stopped twenty-six minutes later. No reactions to trasentine were experienced.

*Phenobarbital.*—Phenobarbital was given orally in the sedative dose of 32.5 mg. to 5 patients and 65 mg. to 1 patient. Hypnotic effects were not desired. Two patients had ileal stomas and 4, colonic stomas. The drug did not modify the tone or the motility of the intestinal tract. Four of the patients slept soundly after administration of phenobarbital; however, no other effects were observed.

*Ephedrine.*—Ephedrine was given by mouth in the amount of 25 mg. to 4 patients. Two had ileal stomas, 1 a colonic stoma and 1 did not have a surgical stoma. In the last case the tandem apparatus was inserted high into the rectum. In 2 cases ephedrine produced no effect on the intestinal tract. In the other 2, however, after a latent period of twelve and sixteen minutes, the tone of the intestine was depressed for twenty and thirty-five minutes (fig. 3). There was no alteration of motility.

*Atropine.*—Atropine was given by mouth on five occasions to 4 patients in doses of 0.65 or 1.3 mg. One patient had an ileal stoma and 4 had colonic

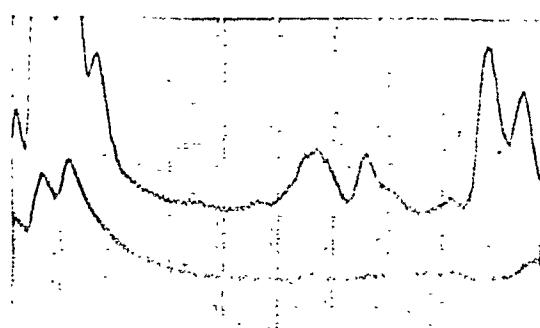


FIG. 3. Effect on the descending colon of 25 mg. of ephedrine given sixteen minutes previously. The decrease in tone which persisted for thirty-five minutes may be noted. There was no effect on motility.



FIG. 4. Inhibition of motility in the descending colon. Tracing from proximal segment is above and from distal segment below. Interval between vertical white lines is thirty seconds. Atropine 1.3 mg. had been given twenty-one minutes previously. Motility was abolished for eleven and a half minutes. There was no decrease in tone below control level. The tiny fluctuations are respiratory in origin.

stomas. The size of the dose did not appear to be related to the response to the drug. No effect on tone was observed. In all instances, after a latent period of twenty-one to forty-two and a half minutes, motility was either completely abolished (fig. 4) or was diminished for intervals of eight to twenty-seven minutes. No contractions of type III appeared during the intervals of diminution of motility; type II waves were diminished in amplitude and were less frequent; type I contractions were not affected by this drug. Three of the patients noticed slight xerostomia; no other side effects were experienced.

Atropine in a dose of 1.3 mg. was combined with 32.5 mg. of phenobarbital

and given to a patient who had an ileal stoma in a sixth study. After a latent period of thirty-two minutes, the amplitude and frequency of contractions were diminished for seven minutes. Tone was not affected.

Atropine in a dose of 1.3 mg. was combined with 25 mg. of ephedrine and given orally to a patient who had an ileal stoma in the seventh study on the effects of atropine. After a latent period of thirty-two minutes, the intestinal tone decreased significantly, and the amplitude and frequency of contractions were diminished in the manner that has been described. The effect was still present when the study was discontinued forty-five minutes later.

#### COMMENT

Numerous competent observers have found that the preparations under consideration exert inhibitory effects on the intestinal tract when administered parenterally. This present study has shown that, with the exception of amethone, the synthetic preparations are ineffective when administered by the oral route in their recommended doses; the natural alkaloids alone alter tone or motility but do not depress the two simultaneously except when atropine and ephedrine are administered together. It is logical to inquire concerning the differences between this and previous investigations. Why are the majority of these drugs ineffective when given by mouth, yet effective when given by the parenteral route?

There are probably three principal reasons for the discrepancy. 1. It is clear than an effective concentration of a drug may be obtained in the body after parenteral administration of the doses used in this study. It is quite possible that these recommended doses are not large enough to allow the production of an effective concentration after oral administration. Contributing to this factor are the possibilities (a) that absorption from the intestinal tract is incomplete so that the entire amount administered is not available, and (b) that absorption may be so gradual and prolonged, and the destruction of the preparation so rapid that an effective concentration cannot be attained. These drugs, however, are said to be promptly absorbed from the intestine. 2. It is unlikely that acetylcholine released intracellularly by the parasympathetic nerves is prevented by these preparations from accomplishing its usual excitatory effects, particularly in the face of concentrations which obtain after oral administration. 3. Parasympathetic inhibition does not necessarily result in domination of the sympathetic impulses. If the inhibitory sympathetic impulses do not become dominant, it is highly likely that much of the inhibitory effect of a preparation is lost.

In support of the last statement is the augmented effect of atropine given in conjunction with ephedrine over that of atropine alone. This combination was the most effective of all preparations tried, and was the only one which

depressed both tone and motility. It is probable that the effect was achieved by the addition of the sympathomimetic action of ephedrine to the parasympathetic depressing function of atropine. This combination is not recommended therapeutically because of the side actions inherent in each drug.

It should be noted that with the exception of the ephedrine and atropine combination, the longest period that motility or tone was reduced or abolished was twenty-seven minutes and thirty-five minutes respectively. These intervals agree fairly closely with the figures given by others in regard to effects of antispasmodic drugs. It appears that long-acting antispasmodics are not available for therapeutic use.

It is possible that larger amounts of these preparations would have yielded more positive results. No attempt was made to determine whether progressively increasing amounts would finally inhibit the motility and tone of the bowel. This study was concerned only with recommended therapeutic doses and their effects or lack of effect.

It is not known whether drug-induced motility corresponds to that present in pathophysiologic conditions. If some agent had been administered to augment motility, the effects of any drug would have to be qualified in the light of the fact that the drug was of value in producing these effects on an intestine artificially stimulated by some agent. The possibility that the tandem system itself acts as a stimulus cannot be excluded. One patient with chronic ulcerative colitis on whom we studied the effects of several drugs presented a bowel markedly overactive as the result of disease. It is of interest that her responses did not differ from those of the group as a whole. The hypermotile colon was not inhibited by novatrin, phenobarbital, trasentine or pavatraine. Amethone abolished this hyperactivity for twenty-two minutes; however, a moderately severe reaction occurred from its use. Unfortunately, neither ephedrine nor atropine were given to this patient.

To each of the drugs included in this investigation has been ascribed by others the common ability to diminish the tone and abolish the motility of the gastrointestinal tract. This combination of effects provides a so-called antispasmodic action. Disregarding for the moment the results of our study, let us ask, what would be the net result in the human being if these preparations succeeded in accomplishing a full antispasmodic effect when given by mouth? Quite obviously, functional paralytic ileus would be produced. The intestine would be made both atonic and nonmotile, in effect, paralyzed. Such a state is no more normal or desirable than the supposed hypermotility and spasm which occasion the use of these drugs. Since all portions of the gastro-intestinal tract probably are influenced by the drugs studied whenever effective concentrations are reached, there is no reason to believe that localized spasm, hypermotility, or irritability are affected to the exclusion of the remainder of

the intestine. Since it is likely that a full antispasmodic effect is produced whenever effective doses are given, it is also doubtful whether a hyperactive bowel is "soothed" to normalcy by these agents. It is questionable whether indications for producing paralytic ileus for therapeutic purposes arise frequently in the human being.

As already discussed, certain motor disturbances are known to exist in the bowel and others probably arise there. Although they are rarely recognized as such, these are specific abnormalities and deserve specific treatment. At present, no preparations are available which are specifically designed to correct these abnormalities. Every effort should be made to develop such badly needed drugs. Ideally, the physician should be able to determine the type of disturbance present, and then provide a specific drug which when administered orally, would be effective in the specific disorder.

No immediate explanation is forthcoming in regard to the failure of atropine to reduce tone and to the lack of motor inhibition following use of ephedrine. Possibly with larger amounts of each these effects would have been achieved.

Administration of both novatrin and trasentine was followed by an increase in tone in 1 instance each. Both of these occurrences were in the patient who had chronic ulcerative colitis. Whether these changes in tone represent idiosyncrasies to the drugs, we cannot say. Such rises never appeared on the numerous control tracings made of this patient. If the increased tone be interpreted as a natural fluctuation, it is obvious that neither preparation was capable of preventing it. In either event, this patient obtained results directly opposite from what would have been expected from use of trasentine and novatrin.

Although amethone succeeded in inhibiting the motility in 3 of 10 instances in which it was given to 8 patients, the 30 per cent incidence of reactions following its use precludes its therapeutic administration.

#### SUMMARY

An attempt was made to alter human intestinal motility by giving amethone, octin, NU-72-4D, pavatrione, syntropan, trasentine, phenobarbital, ephedrine and atropine by mouth in their recommended therapeutic doses. Of the synthetic preparations, only amethone inhibited motility and this in 3 of 10 studies on 8 patients. The 30 per cent incidence of reactions following amethone precludes its therapeutic use. No depression of tone was produced by any of the synthetic preparations. An increase in tone was found in 1 instance each after administration of novatrin and trasentine.

Atropine was consistently effective in either depressing or abolishing motility; it had no demonstrable effect on tone. Ephedrine reduced tone in 2 of 4 cases studied without altering motility. A combined parasympathetic depressant

and sympathomimetic effect was achieved by giving atropine in conjunction with ephedrine. This combination provided the only instance in which both tone and motility were depressed. The combination is not suggested for therapeutic use.

In no instance was any effect noted on the intersegmental relationships and effects of all drugs were transient.

A plea is made for the development of preparations which may be specifically employed for the correction of specific motor disturbances of the bowel. Such drugs should be effective by mouth and should be longer acting than preparations now available.

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## DISCUSSION

DR. JULIUS COMROE (Philadelphia, Pa.): Dr. Posey has made clear several important points:—First, that drugs to be used for their effects upon the human gastro-intestinal tract must be evaluated finally upon the *human* gastro-intestinal tract; animal experimentation alone cannot be relied upon since upon occasion this has proved to be misleading qualitatively as well as quantitatively. Second, that drugs to be given orally must be evaluated, particularly from the quantitative point of view, by the effects they produce upon the gastro-intestinal tract following oral administration. Too often we determine the effectiveness of a drug given by parenteral routes and use this dosage orally without any real idea as to the rate and completeness of absorption of the drug given orally. For example, 0.25 to 0.5 gram of aminophylline is required by the intravenous route to relax bronchial spasm (in asthma) but the U.S.P. dose for oral administration is only 0.2 gram. (It would be of interest to determine the effectiveness of antispasmodics by oral and parenteral administration upon the same patients, if possible.) Third, that drugs to be used orally for the relief of hypermotility or increased tone should be evaluated whenever possible upon patients with hypermotility or increased tone.

It would be of interest for three reasons to evaluate the effect of drugs upon widely different portions of the gastro-intestinal tract at the same time by multiple balloons: (1) The effect of parasympathetic stimulants and possibly of parasympathetic blocking agents is most pronounced in the upper gastro-intestinal tract. (2) The upper tract can influence the motility of the lower merely by moving contents along more swiftly and so providing the stimulus of distention. It has recently been reported that changes in ureteral motility parallel the amount of urine formed per minute; in other words the presence or absence of distention is a more potent factor in ureteral peristalsis than drug actions. (3) We need more information regarding the action of drugs upon sphincters. We are accustomed to think that the autonomic nervous system has one effect upon the gut with diametrically opposite effects upon sphincters. If classical pharmacological concepts are correct, parasympathetic stimulants should relax sphincters and parasympathetic blocking agents should contract them; yet we use atropine to relieve "pylorospasm" and there are reports that the prolonged use of DFP (a parasympathetic stimulant) has produced cardiospasm.

DR. STEWART WOLF (New York, N. Y.): I agree with Dr. Comroe that this paper of Dr. Bargen, Dr. Posey, and Dr. Code is important as an experimental study applied to human beings. Dr. William Grace at Cornell, has had the opportunity of studying the effects of several of these so-called antispasmodic agents on two subjects with large exposed colons, one with an evaginated colon about a foot long on the right side,

and one with a similar-sized lesion on the left. His observations confirmed in general the findings of Dr. Posey.

Mouth administration of these agents did not bring about a decrease in tone or a decrease in motility. Indeed, on an occasion when the subject resented the procedure, the administration of the agent was followed actually by an increase in tone and motility. Even with atropine, 2 mg. in one of the fistulous subjects, a marked shrinkage of the colon with increased peristaltic waves was induced during a period of strong resentment against this injection, which was made with a hypodermic needle.

From these experiences and from the data which have been presented to us, we can conclude that the available antispasmodics are not very important therapeutic tools for the regulation of colonic activity and, as has been pointed out, we had better first determine the type of control we wish to exert over the colon. This will require experiments such as Dr. Bargen has shown us, carried out before, during, and after episodes of so-called spastic states and other disturbances.

We are indebted, then, to the essayists for pointing out this apparently simple, rational, physiologic approach to diseased states in the gastro-intestinal tract, encouraging us to turn from empiricism to inquiry.

**DR. E. LEONARD POSEY** (Rochester, Minn.): Dr. Comroe rightly stated it would probably be better if these drugs were studied under conditions of hypermotility. We have had the opportunity in only one instance of studying the effect of these drugs under such conditions. We had a patient upon whom a colostomy had been performed for chronic ulcerative colitis. Unfortunately, it had been performed in an area of active disease. This patient's bowel was markedly overactive.

This patient's responses did not differ markedly from that of the group in their reactions to pavatrine, phenobarbital, cinchophen, and novatropine. There was no effect exerted by these drugs upon this patient's bowel. Amethone inhibited the motility without producing a drop in tone. It was this patient who got the severe reaction following this drug.

## THE INHIBITION OF THE SHWARTZMAN PHENOMENON BY ANTIHISTAMINE AND VITAMIN P-LIKE SUBSTANCES

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Since the discovery of the "phenomenon of local tissue reactivity" by Shwartzman in 1927, repeated attempts have been made to explain certain conditions in human pathology by this mechanism; including hemorrhagic-necrotic skin reactions<sup>7,24</sup>, extensive gangrene following administration of horse serum<sup>11</sup>, putrid abscesses of the lung<sup>5</sup>, and recurrent hemorrhage in peptic ulcer<sup>6</sup>. In nonspecific ulcerative colitis this mechanism has been suspected to be responsible for the continuation or exaggeration of the process<sup>27,19</sup> and even for the primary lesion<sup>18</sup>. Hemorrhagic pancreatitis and infarctions of internal organs may also fall into this category. In addition, the following conditions have been explained by the general Sanarelli-Shwartzman reaction: deaths following typhoid vaccine therapy<sup>25,16</sup>, purpuric meningococcemia and the Waterhouse-Friedrichsen syndrome<sup>2</sup>.

Although this explanation still remains speculative, we believe it is important to investigate factors which affect the presence of the Shwartzman reaction. The same modifying factors can also be applied in the prophylaxis and therapy of the above mentioned conditions.

The Shwartzman reaction is a phenomenon of hypersensitivity and has as its most prominent anatomical feature markedly increased capillary fragility. Accordingly two groups of substances were used in our trials to inhibit its occurrence: antihistamine compounds and vitamin P-like substances.

Two papers on the effect of antihistamine drugs on the Shwartzman reaction reported equivocal results: Boquet<sup>3</sup> administered Antergan in a dose of 20 mg. intravenously 15 min. previous to the precipitating injection of filtrate in 3 rabbits and did not observe any definite inhibition. By contrast Bovet and Walther<sup>4</sup> used the compound 2786 R.P. (N-p-methoxybenzyl N-dimethylaminoethyl α amidopyridin) intravenously 30 min. prior to and 3, 6, and 10 hours after the precipitating injection, the total dose being 7.5 mg./kg. body weight in 20 rabbits; they reported definite inhibition of the Shwartzman reaction in 65 per cent of the animals.

To our knowledge the effect of vitamin P on the Shwartzman phenomenon has not yet been studied.

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## METHOD

"Agar washings filtrate" was prepared according to Shwartzman<sup>23</sup> from cultures of two strains of *E. coli communis* and two strains of *E. coli communior*. These were incubated for 48 hours on Kolle flasks containing plain agar, pH 7.3 and placed in the boiling water bath for 10 min. before being filtered through a medium Berkefeld candle. This filtrate contained 400 reacting units per cc.

One hundred and two white rabbits of both sexes weighing from 3 to 5 pounds were used in our study. Each rabbit received a single intradermal injection of 0.25 cc. of filtrate diluted with an equal amount of saline. The injection was made into the middle part of the abdomen close to the median line; the hair was previously cut by an electric clipper. Twenty-four hours after this preparatory injection a precipitating injection of 4 reacting units was made intravenously. The results were read after 5 hours.

Animals were divided into 9 groups. Eight groups of 10 rabbits each were treated with various drugs, the ninth group of 22 rabbits serving as controls.

Group I: 10 mg./lb. body weight of a 1% aqueous solution of Benadryl† was given orally 45 min. prior to and 2½ hours after the precipitating injection of filtrate.

Group II: 1.5 mg./lb. body weight of a 0.5% suspension of Benadryl in saline was injected intravenously 5 to 10 min. previous to and 2 hours after the precipitating injection.

Group III: 10 mg./lb. body weight of a 1% aqueous suspension of Neo-Antergan† was administered orally 45 min. previous to and 2½ hours after the precipitating injection of filtrate.

Group IV: 5 mg./lb. body weight of a 1% aqueous suspension of rutin† was given orally for two days. The third day the same amount was administered in two separate doses; the preparatory injection of filtrate was given with the first of them. On the fourth day the same doses of rutin were administered 45 min. previous to and 2½ hours after the precipitating injection of filtrate.

Group V: 1 cc./animal of methyl-glucamine salt of rutin† containing the equivalent of 25 mg. of rutin was injected intravenously 5 to 10 min. prior to and 2 hours after the precipitating injection of filtrate.

Group VI: 20 mg./lb body weight of a 5 per cent suspension of hesperidin methyl chalcone† was administered intravenously 5 to 10 minutes previous to and 2 hours after the precipitating injection of filtrate.

Group VII: 1 cc./animal of citrin† (containing 40 mg. of neohesperidin in

† We are grateful to the Parke, Davis & Co. for the supply of Benadryl; to the Merck & Co. for Neo-Antergan; to Dr. J. F. Cough, Eastern Regional Research Laboratory for rutin; to Dr. M. B. Plungian, Temple University for methyl-glucamine salt of rutin; to the California Fruit Growers Exchange for hesperidin; and to the Hoffmann-La Roche, Inc. for citrin.

a 30% solution of sarcosin anhydride) was given intravenously 5 to 10 min. previous to and 2 hours after the precipitating injection of filtrate.

TABLE 1  
*The results of Shwartzman reaction after administration of drugs*

GRADING OF THE SHWARTZMAN REACTION	1 STRONG REACTION	2 MILD REACTION	3 PETECHIAE ONLY	4 NO REACTION	TOTAL
I. Benadryl orally	2	1	4	3	10
II. Benadryl intravenously	6	1	1	2	10
III. Neo-Antergan orally	4	2	3	1	10
IV. Rutin orally	3	4	1	2	10
V. Rutin intravenously	4	2	2	2	10
VI. Hesperidin intravenously	4	0	1	5	10
VII. Citrin intravenously	6	1	2	1	10
VIII. Benadryl orally + citrin i.v.	3	1	3	3	10
IX. Controls	20	0	0	2	22



FIG. 1

Group VIII: These animals were treated simultaneously with oral Benadryl and intravenous citrin using the same dosage as in the experiments with the individual drugs (Groups I and VII).



FIG. 2



FIG. 3

Group IX: Control animals received only the injections of filtrate. Two to three control animals were tested simultaneously with each treated group.

#### RESULTS

The results are summarized in Table 1.

The following grading of the reaction was adopted: Grade 1. Massive hemorrhage larger than 1 x 1 cm (Fig. 1). Grade 2. Hemorrhage smaller than 1 x 1 cm (Fig. 2) or mild scattered reaction of any size (Fig. 3 and 4). Grade 3. Petechiae only. Grade 4. No hemorrhage.

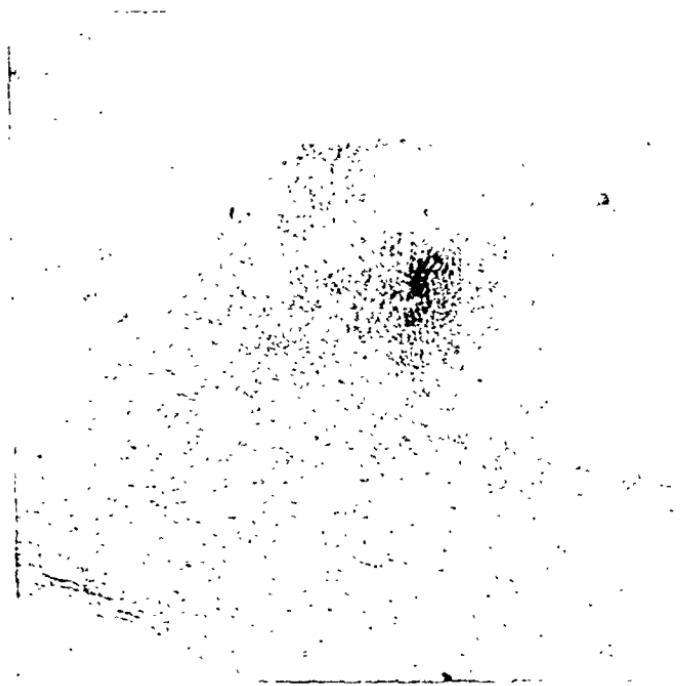


FIG. 4

#### DISCUSSION

Ninety one per cent of control animals showed massive large reactions. The negativity of the result in the remaining 9% may be explained by a natural immunity. This fact suggests that minute and scattered reactions in treated animals are a relatively more reliable indicator of an inhibition than negative results which may be due either to complete inhibition or the immunity.

All the drugs which have been employed showed an inhibitory effect, with decreasing order of potency approximately as follows: Benadryl orally, rutin orally, Neo-Antergan orally, rutin intravenously, hesperidin intravenously, citrin intravenously, Benadryl intravenously. The addition of citrin did not increase the effect of oral administration of Benadryl. It is possible that the

differences between oral and parenteral administration of the various drugs studied might be due to dosages employed, since larger doses were used orally.

There are three possible explanations for the inhibitory effect of the antihistamine compounds on the Shwartzman phenomenon: 1. They may increase capillary resistance per se. 2. They may potentiate the effect of epinephrine in increasing capillary resistance. 3. They may prevent the action of histamine in increasing capillary permeability<sup>12, 15, 20</sup>. The latter explanation would seem the most plausible in view of the data available since antihistamine drugs diminish the effects of histamine on capillary permeability but fail to diminish effects of other substances<sup>15</sup>.

The vitamin P-like substances increase the capillary resistance<sup>28, 1</sup> possibly by inhibition of auto-oxidation of epinephrine<sup>26, 13, 11</sup>. They also have an anti-allergic effect since they prevent anaphylactic shock<sup>22, 8</sup> and serous inflammation<sup>9</sup>. Rutin not only prevents increased capillary permeability due to histamine, but also that due to chloroform and negative pressure<sup>1</sup>. The effect of rutin on the capillaries, whether direct or indirect through facilitation of the influence of epinephrine, is probably not specific as appears to be the case with antihistamine drugs.

Antihistamine compounds have been used in the treatment of peptic ulcer<sup>21</sup> and chronic ulcerative colitis<sup>10</sup> with uncertain results. Citrin has been reported to control the development of the early stages of nonspecific ulcerative colitis<sup>17</sup>.

A more thorough study of the effect of all these drugs in the conditions possibly related to the Shwartzman phenomenon might throw considerable light on their pathogenesis.

#### SUMMARY

1. A study was made to determine the effect of various antihistamine and vitamin P-like substances on the development of the Shwartzman phenomenon.

2. The administration of Benadryl, Neo-Antergan, rutin, hesperidin and citrin has been shown to exert an inhibitory effect on the production of this phenomenon.

3. A possible application of these drugs in the prophylaxis and treatment of the conditions which might be related to the Shwartzman reaction is suggested.

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## AMEBIC PLEURAL EFFUSION

## CASE REPORT

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In a statistical survey of amebiasis in 1945, among the complications we encountered a single instance of pleural effusion. This publication<sup>1</sup> did not permit a discussion of individual cases; we consider the relative rarity of such a form of metastatic amebiasis to justify this case report. With hematogenous amebic dissemination accepted<sup>2</sup> almost any metastatic site is conceivable and seemingly has been encountered: perinephritic<sup>3</sup>, splenic<sup>4</sup>, uterine<sup>5</sup>, cerebellar<sup>6</sup>, gall bladder, bone and pericardium<sup>2</sup> are among the unusual. These rarer metastatic amebic manifestations occur secondary to the more common complication, metastatic amebic hepatitis<sup>7</sup> in most instances. Akenhead<sup>8</sup> states that 75 per cent of amebic pleuropulmonary involvements result from rupture of an hepatic abscess, that the remainder are of hematogenous etiology. We find no mention of proven amebic pleural effusion without demonstrable amebic hepatitis or pneumonitis. The literature abounds with pleural effusions as a concomitant to amebic hepatic abscess with subphrenic and pleuropulmonary involvement. The isolated pleural involvement in the accompanying case report is presumed to be a hematogenous isolation to the right pleural cavity embolic from an intestinal focus.

## CASE REPORT

Case A. P. Z. A 39 year old artisan was first seen January 2, 1941 complaining of severe diarrhea persistent for three months. The stools, watery and copious, were often sanguinopurulent. Tenesmus, low grade fever and fifty pound weight loss were encountered in the review of symptoms.

Pertinent to the past history was an acute episode of amebic dysentery in 1931, inadequately managed. Physical examination showed apparent illness and weight loss, but was otherwise insignificant.

Proctosigmoidoscopy rendered a diagnosis of severe amebic ulcerative colitis.

The amebic colitis responded well to carbarsone followed by Anayodin. Emetine was apparently not indicated. Proctosigmoidoscopic examination proved healing in the visualized segment. Five stool studies at monthly intervals were negative. The patient was considered cured and was discharged June 10, 1941.

On 9/20/41 he entered Touro Infirmary (T-9083) with admission findings suggesting a diagnosis of lobar pneumonia (right basal) with pleural effusion. This was an acute illness of ten days' duration. There was no significant interval history.

There was a mild leukocytosis. Stool studies were negative. There was no productive cough.

Roentgen findings were those of a massive right pleural effusion. There was no characteristic disturbance in diaphragmatic configuration.

Amebic hepatitis with possible subphrenic abscess and trans diaphragmatic communication was suspected. Despite absence of localized pain, the right lobe of the liver and subdiaphragmatic space were explored by needling with negative findings. X-ray repeated after thoracentesis, with removal of 3200 cc. of thick reddish brown serosanguineous fluid, showed lobular atelectasis, evidence of pleural thickening, residual effusion and the suggestion of a subdiaphragmatic abscess, but no hepatomegaly nor any etiologic pneumonic process. Immediate microscopic examination of the pleural fluid showed endameba histolytica trophozoites; the cytologic study of the fluid showed a minimal neutrophic response. Stool studies were negative for endameba. The pleural fluid was sterile on repeated cultures.

Emetine, one grain intramuscularly, and pleural space lavage with 5 grains of Emetine hydrochloride in 500 cc of saline daily for eight days was given. The patient improved, no endameba histolytica were demonstrated in the effusion fluid after the second day. The patient was discharged 9/28/41.

Readmission 10/6/41 was occasioned by recurrent massive pleural effusion. Endameba histolytica were demonstrated in the pleural fluid on two occasions, which fluid simulated that of the previous admission. Again stool studies were negative. Roentgen studies, including bronchography, were not informative. Thoracentesis every third day with Emetine lavage of the pleural space was performed on ten occasions. Diodoquin was given orally. The patient was released from the hospital 11/1/41.

No further thoracentesis was indicated. Pleural fluid, however, was examined at ten day intervals for sixty days; no endameba were demonstrated. Persistent pleuritis and minimal effusion were roentgenologic findings for seven months. Compression atelectasis of the right lung resulting from progressive pleural thickening and constriction became demonstrable thereafter. No subdiaphragmatic involvement developed.

The patient had no recurrence of amebiasis. The pleural thickening has resulted in decreased vital capacity to half estimated normal, mild cor pulmonale, compensatory left pulmonary emphysema, polycythemia and clubbing of the fingers and toes.

*Comment:* An interesting instance of amebic pleural effusion, assumed embolic from an intestinal focus without other demonstrable extraintestinal amebiasis is reported. We cannot, however, entirely rule out the possibility of an amebic interstitial pneumonitis.

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## ANNULAR PANCREAS

### DESCRIPTION OF A CASE

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Annular pancreas is a rare anomaly in which the second part of the duodenum is surrounded or almost completely surrounded by pancreatic tissue. According to Lehman<sup>1</sup> the condition was first described by Tiedeman in 1818. In 1933 McNaught<sup>2</sup> reported a case and gave references to thirty-nine other cases in the literature. By 1935 McNaught and Cox<sup>3</sup> had seen another case themselves and had found three more in the literature. Since then cases have been reported by Weissberg<sup>4</sup>, Truelson<sup>5</sup>, Cunningham<sup>6</sup>, Lehman<sup>1</sup>, Chapman and Mossman<sup>7</sup>, Gross and Chisholm<sup>8</sup>, Custer and Waugh<sup>9</sup>, Stofer<sup>10</sup> and by Goldyne and Carlson<sup>11</sup>. For the most part these are records of post mortem findings, but in thirteen cases the discovery was made at operation and Lehman<sup>1</sup> made a provisional diagnosis of annular pancreas preoperatively.

### CASE HISTORY

E. K. No. 46/8549, a fifty-three year old housewife was admitted with a history of heartburn and flatulence for the previous five years. These symptoms were mild and were brought on by eating spices or highly seasoned foods. Nine months before admission she was seized with severe epigastric pain which was partially relieved by vomiting but finally required morphine. After six months a similar attack occurred and subsequent investigation in another hospital revealed cholelithiasis. Cholecystectomy was performed and the surgeon reported that the common bile duct was patent and free of stones. Three weeks after operation the severe mid-epigastric pain returned, and attacks then occurred at intervals of a few days over a period of four weeks, at the end of which time she was admitted to the Kingston General Hospital. The pain was extremely severe, at times spread in a band-like fashion around her waist radiating to the back, and frequently required morphine for relief. On one occasion she vomited coffee-ground-like material and the day before admission she passed a tar-coloured stool. There had been a loss of weight amounting to 20 pounds since her cholecystectomy. Her past medical history and her family history contained nothing relevant.

She was a short, placid woman with a lemon-tinted skin who still weighed 190 pounds. There was a scar of a recent right upper paramedian incision on her abdominal wall and on deep palpation a firm, non-tender mass the size of a golf ball could be felt under the right costal margin. This mass moved with the liver, which was not palpably enlarged. There was tenderness in the mid-epigastrium. Otherwise there were no abnormal findings. Blood pressure 135/75. Her urine contained no bile, even during episodes of pain, and was free of other abnormal constituents. Hemo-

globin 11.6 Gm.%, R.B.C. 4,510,000 per cu. mm., W.B.C. 4,200 per cu. mm. with 39% neutrophils, 1% eosinophiles, 59% lymphocytes, and 1% mononuclear cells. Sedimentation rate 29 mm. in 1 hour. Wassermann negative. Fasting blood sugar 91 mg.%, Blood urea 44 mg.%. Serum cholesterol 284 mg.%. Plasma bilirubin 1.04 mg.%. Two hours after the onset of a severe attack of pain, the plasma bilirubin was 2.4mg.%. Occult blood in stools and in gastric contents +++. Electrocardiogram essentially normal. Radiography after barium meal showed a filling defect in the right side of the second part of the duodenum, suggestive of extrinsic pressure. There was no x-ray evidence of stone in the region of the common bile duct. During an intravenous pyelogram only the upper calyx was seen on the right side; the left side filled normally. Preoperatively the patient ran a low grade temperature.

The diagnoses which were entertained preoperatively were (a) annular pancreas (b) duodenal ulcer with perforation (c) stone in the common duct and (d) neoplasm. Because of the recent laparotomy further surgery was undertaken reluctantly but about three weeks after the patient's admission to hospital it became imperative because of the severe pain and the continued blood loss. When the abdomen was opened an encapsulated hematoma was found in the free edge of the lesser omentum and the second part of the duodenum was found to be embraced by a band of pancreatic tissue about one and a half inches wide and one-half inch thick which caused moderate narrowing of the duodenum. The band was sectioned and the stumps of pancreatic tissue were ligated. It was thought necessary to be sure that the common duct was free of stones and as it was impossible to identify it the duodenum was opened and a sound passed up the entire length of the common duct and for three inches along the pancreatic duct without any obstruction being encountered. The patient's temperature rose gradually after operation and despite penicillin continued to be elevated. A week postoperatively she developed pain in the right lower thoracic region and on the tenth postoperative day a large subdiaphragmatic abscess was evacuated. Soon after this it was evident that a duodenal fistula had formed, and on the twenty-second post-operative day a posterior isoperistaltic gastrojejunostomy was performed. The patient died two days later.

At autopsy the common bile duct was found to be dilated but the ampulla was patent and no stones were present. Aside from the stumps of pancreatic tissue which still partially embraced the duodenum, the pancreas was not unusual in its gross appearance. The section of pancreas removed at operation was normal microscopically and showed no increase in fibrous tissue or leucocytic infiltration. Sections of the material obtained at autopsy showed mononuclear infiltration of the fibrous tissue at the periphery. The liver sections showed some widening of the sinusoids without any concomitant congestion, and moderate vacuolation of the liver cells in the peri-portal areas.

#### DISCUSSION

An annular pancreas is simply a band of secreting pancreatic tissue which passes around the duodenum, usually in its second part, although occasionally

the third part of the duodenum has been involved. If the ring is incomplete, it will take the form of two arms reaching out from the pancreatic head, partially encircling the duodenum and leaving a gap on the ventral surface which is filled in with loose fibrous tissue. The majority opinion concerning the mode of origin of the anomaly is that it occurs as the result of the failure of complete migration of the ventral anlage of the gland first to the right and then posteriorly to the duodenum to fuse with the dorsal anlage. Because of this, a tip of the ventral anlage remains in an anterior position while the duct outline rotates around the duodenum in a normal manner. In consequence the band of pancreatic tissue becomes wrapped about the duodenum in a napkin-ring fashion and the duct from the ventral bud sweeps around the duodenum to enter the Duct of Wirsung. Others (Lerat<sup>12</sup> and Weissberg<sup>4</sup>) have suggested that the annular arrangement is the result of hyperplasia of pancreatic tissue which dissects its way beneath the serosal coat of the duodenum eventually to surround it. Lerat interprets this as a regenerative process following fetal peritonitis.

Because of their importance in surgical procedures the ducts of the annulus have been the subject of much investigation. Commonly a main duct begins in the main part of the band anteriorly and to the left of the duodenum, and sweeps around to the right and then behind the duodenum to join the main pancreatic duct. However Cunningham<sup>6</sup> and Stofer<sup>10</sup>, using injection techniques, both reported failure to establish connection between the ductal system present in the annulus and the main pancreatic duct.

It is clear that the condition may never cause symptoms. On the other hand it has been known to draw attention to itself in the neonatal period and as late as the eighth decade. The clinical picture is made up chiefly of the symptoms and signs of acute or recurring duodenal obstruction. When the common bile duct is subject to pressure, obstructive jaundice may result. Chronic or acute pancreatitis may also occur. Peptic ulcer has been noted in association. The roentgenological sign of importance is dilatation of the first part of the duodenum with evidence of extrinsic pressure on the second part.

The only clear indication for surgical intervention is the presence of obstruction of the duodenum or the common bile duct and in that event two main courses are open to the surgeon. Firstly, the obstructing pancreatic band may be directly attacked by simple division on the right lateral aspect of the duodenum where the ducts exist in their smallest caliber<sup>14, 15</sup> or by resection of a portion of the ring<sup>1</sup>. These procedures have been uniformly successful but they bear with them the risk of pancreatic fistulae and the possibility of an underlying atretic duodenum necessitating further surgical reconstruction. Secondly, the obstruction may be overcome by a short-circuiting type of operation such as gastroenterostomy<sup>13, 5</sup> or duodenoejunostomy<sup>8</sup>. These are

standard and satisfactory procedures and the comparatively high mortality associated with them when performed because of obstructive annular bands of pancreas has been due to respiratory infections and other unrelated causes and occurred in the days before sulfonamides and the antibiotics were introduced. In the present case it would undoubtedly have been wiser to do nothing more than divide or excise a portion of the pancreatic ring but because of uncertainty regarding the complete patency of the common bile duct, exploration of the duct was deemed necessary. The duodenal fistula which followed was possibly the result of auto-digestion both from within and without.

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## ACUTE HEMORRHAGIC PANCREATITIS

STUDY OF A PATIENT HAVING DISSEMINATED FAT NECROSIS, HYPOCALCEMIA, HYPOPOTASSEMIA, UREMIA, DIABETES MELLITUS, ASCITES AND BILATERAL HYDROTHORAX

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The following case of acute hemorrhagic pancreatitis is reported because of the numerous complications and the unusual opportunity for study of the behavior of calcium, potassium and certain other chemical constituents of the blood, ascitic and pleural fluids during life and for study of the calcium and potassium content, determined post mortem, of tissues affected by fat necrosis.

### REPORT OF CASE

A white man fifty-five years of age came by ambulance to the Mayo Clinic on November 21, 1946, because of an attack of severe abdominal pain of thirty hours' duration. Since 1936 he had suffered from approximately six episodes of moderately severe pain located across the upper and middle parts of the abdomen and spreading around the sides of the abdomen to the back at the corresponding level. During attacks the pain was most intense below the left costal margin, persisted for several hours and was accompanied by abdominal distention. Some of the attacks were severe enough to require the hypodermic injection of morphine. During some of the episodes the color of the urine became dark. There were numerous minor spells, some of which would awaken him at night which consisted of a feeling of fullness in the epigastric region but which did not require the use of opiates. In the interval between attacks he complained of a sense of epigastric fullness, gaseous distress and belching after meals, particularly after the ingestion of greasy foods.

The last attack occurred on November 20, 1946, when, after breakfast, he was suddenly seized with a very severe pain in the upper part of the abdomen which spread all over the abdomen and around both sides to the lumbar region. There were pallor of the skin, profuse perspiration, dark-colored urine, nausea, vomiting and abdominal distention. Hypodermic injection of morphine was required on three different occasions without affording relief of the pain. Intermittent hiccup supervened.

On admission to the hospital, thirty hours after onset of the attack, he was experiencing severe abdominal pain. Marked dehydration, hiccup, perspiration, considerable generalized abdominal tenderness and spasm and a limited degree of ascites were observed by the admitting physician. No peristaltic sounds were audible. The systolic blood pressure was 145 and the diastolic 95, expressed in millimeters of mercury, the pulse rate 128 and the temperature 102° F. The leukocyte count was 11,000 per cubic millimeter of blood and the sedimentation rate was 5 mm. in one hour (Westergren method).

On the morning after admission, approximately forty-eight hours after onset of the attack, the concentration of amylase in the serum was 2,666 units (normal 0 to 320). Abdominal pain was still present, ascites was more pronounced and there was abdominal distention, but flatus was being passed. On the fourth day of the attack, the value of amylase in the serum was 1,600 units; the value for serum lipase, 1.3 cc. of tenth-normal potassium hydroxide per cubic centimeter of serum; the concentration of urea in the blood, 168 mg. per 100 cc.; the fasting blood sugar, 340 mg. per 100 cc.; the carbon dioxide combining power of the plasma, 39 volumes per cent; the concentration of chlorides in the plasma, 567 mg. per 100 cc. On the third day of the attack the concentration of bilirubin in the serum was 0.7 mg. of direct and 1.7 mg. of indirect reacting bilirubin per 100 cc. according to the van den Bergh reaction. Roentgenograms of the chest were noncontributory. Abdominal pain was almost gone but generalized abdominal tenderness and spasm persisted.

On the sixth day of the attack, ascites and abdominal distention had increased and four loose, grossly bloody stools were passed. The sedimentation rate had increased to 88 mm. and the serum amylase had decreased to 160 units.

Several bloody stools were passed on the eighth day of the illness. Fluids were being taken orally, but due to increasing abdominal distention it became necessary to institute intermittent aspirations from the stomach and upper part of the small bowel. On this day the concentrations of calcium and phosphorus in the serum were respectively 5.7 and 2.7 mg. per 100 cc. The concentration of protein on the tenth day of illness was 5.3 gm. per 100 cc. of serum and the albumin-globulin ratio was 1.29 to 1.0.

During the remaining days of the patient's illness there was increasing abdominal distention and ascites, the concentration of blood urea and blood sugar remained elevated and the tongue continued to be dry even though there was a daily oral and parenteral intake of fluids varying from 3,000 to 7,500 cc.

Efforts were made to maintain a proper balance of fluids and electrolytes by the intravenous administration of 5 and 10 per cent solution of dextrose in water or in 0.9 per cent solution of sodium chloride, 5 per cent solution of sodium bicarbonate, 10 per cent solution of potassium chloride and 10 per cent solution of calcium gluconate. Regular insulin, one unit for each 5 gm. of glucose in the fluids given intravenously, was administered. A transfusion of 500 cc. of blood was given because of hypoproteinemia.

Hydrothorax became apparent on the right side on the ninth and on the left side on the thirteenth day of the attack. On abdominal paracentesis 1,500 cc. of straw-

TABLE I  
*Blood findings in a case of acute hemorrhagic pancreatitis*

DAY	SERUM						PLASMA			BLOOD		
	Mg. per 100 cc.			Amylase, units	Chlorides, mg. per 100 cc.	$\text{CO}_2$ combining power, per cent	Proteins, gm. per 100 cc.	Albumin-globulin ratio	Hematocrit, per cent erythrocytes	Leukocytes per cu. mm.	Sedimentation rate, mm. in 1 hr.	
	Ca	P	K									
				Lipase, cc. N/10 KOH per cc.								
2												
3												
4												
6												
7												
8	5.7	2.7										
10		10.5	330.0									
11												
12	5.1	4.0	11.0	327.0								
13	5.9	4.0		316.0	350	82						
14												
15	5.1	5.1			94							
16					114							

colored fluid was obtained and on pleurocentesis 1,000 cc. of straw-colored fluid was removed from the right pleural space. This pleural fluid contained 3,500 cells per cubic millimeter and culture revealed *Escherichia coli*. Ascites and hydrothorax quickly recurred to the point of cardiac and respiratory embarrassment.

Increased concentrations of urea and sugar in the blood and the low values for serum calcium and potassium persisted. During the last two days of the patient's illness the urinary output decreased to a low level and there were signs of respiratory

TABLE 2  
*Miscellaneous laboratory findings in a case of acute hemorrhagic pancreatitis*

TYPE OF EXAMINATION	RESULT	DAY OF ATTACK
Pleural fluid		
Amylase, units.....	50	12
Calcium, mg. per 100 cc.....	3.7	12
Cell count per cubic millimeter.....	1,300	13
Protein, gm. per 100 cc.....	2.6	17
Albumin-globulin ratio.....	1.43:1	17
Potassium, mg. per 100 cc.....	8.9	17
Culture ( <i>Escherichia coli</i> ).....	Positive	12
Peritoneal fluid		
Amylase, units.....	50	12
Protein, gm. per 100 cc.....	2.5	17
Albumin-globulin ratio.....	1.57:1	17
Other		
Prothrombin time, seconds	20 (after vitamin K) 19 18	7 14 15
Bromsulfalein retention, grade (1 to 4).....	4	6
Blood culture.....	Negative	15
Fat in a single stool, per cent of dry weight.....	3.7	6
Urine (24 hr. specimen)		
Calcium .....	Trace	14
Phosphorus, mg. in 1,300 cc.....	420	14

and cardiac embarrassment and increasing toxemia. He died on the seventeenth day of the attack.

The various laboratory data are given in tables 1 and 2.

*Necropsy findings.*—Necropsy revealed moderate subcutaneous edema of the legs, back and arms. The body was moderately obese and the panniculus adiposus was 3 cm. thick. The peritoneal cavity contained 3,000 cc. of yellowish fluid mixed with fibrin. The intestinal coils were matted together by fibrinous adhesions. On the small intestine, mesentery, omentum, parietal peritoneum, mediastinal connective tissues and the pleural surface of the diaphragm there were many white and yellow

nodules having the appearance characteristic of fat necrosis. A roentgenogram of the omentum revealed these nodules as areas of increased density. The right and left pleural cavities each contained 250 cc. of clear yellow fluid.

Aside from the collapse of the lower portions of the upper lobes and also of the middle right and both lower lobes, the condition of the lungs was not remarkable.

The spleen was enlarged and weighed 340 gm., compared with an estimated normal weight of 200 gm.

The liver was also enlarged and weighed 2,145 gm., compared with an estimated normal weight of 1,800 gm. Aside from a cyst in the right lobe, which measured 0.5 cm., the liver did not appear abnormal. The gallbladder appeared to be distended and contained about 30 cc. of greenish black bile and more than 100 faceted stones. The latter were mottled black and tan and ranged in size from 1.5 cm. to 0.1 cm. in diameter.

Two small recent ulcers had penetrated into the muscularis on the anterior wall of the stomach. There were several small polypoid lesions measuring up to 0.5 cm. in diameter.

The pancreas was encased in a large hemorrhagic and necrotic mass. It was enlarged and the entire tail and body, as well as a portion of the head of the gland, appeared reddish black and necrotic. There were numerous yellowish nodules of fat necrosis on the surface and in the peripancreatic connective tissue. On longitudinal section of the pancreas the hemorrhagic and necrotic tail and body of the gland were shown to be sharply demarcated from a portion of the head (fig. 1a). In this portion of the head there were numerous foci of fat necrosis. Dissection of the gland revealed necrosis and thrombosis of a large artery supplying the tail and body of the gland.

The common bile duct appeared normal. Dissection of the common bile duct and pancreatic ducts revealed that they were separate up to a point 2 mm. from the orifice at the papilla of Vater.

The perinephric adipose connective tissues were the site of numerous yellowish and hemorrhagic areas of fat necrosis. The combined weight of the kidneys was 490 gm., but aside from their large size they did not appear abnormal.

On histologic examination, in the head of the pancreas there were many areas of parenchymatous necrosis at the periphery of which were collections of polymorphonuclear and mononuclear leukocytes as well as fibroblasts (fig. 1b). The periphery of the necrotic portions took a bluish stain, and staining by the von Kossa method revealed the presence of calcium. In the intact portions of the head of the gland, interlobular fibrosis was marked, but only a few lymphocytes and mononuclear leukocytes were observed (fig. 1c). Squamatization (so-called metaplasia) of the epithelium of a small duct was observed (fig. 2a).

Most of the sections taken from the tail of the pancreas revealed massive necrosis and hemorrhage. A section taken from the region between the body and head of the gland also revealed interlobular fibrosis and necrosis and destruction of a wall of an artery with hemorrhage (fig. 2b).

In sections of the liver there were small collections of polymorphonuclear leuko-

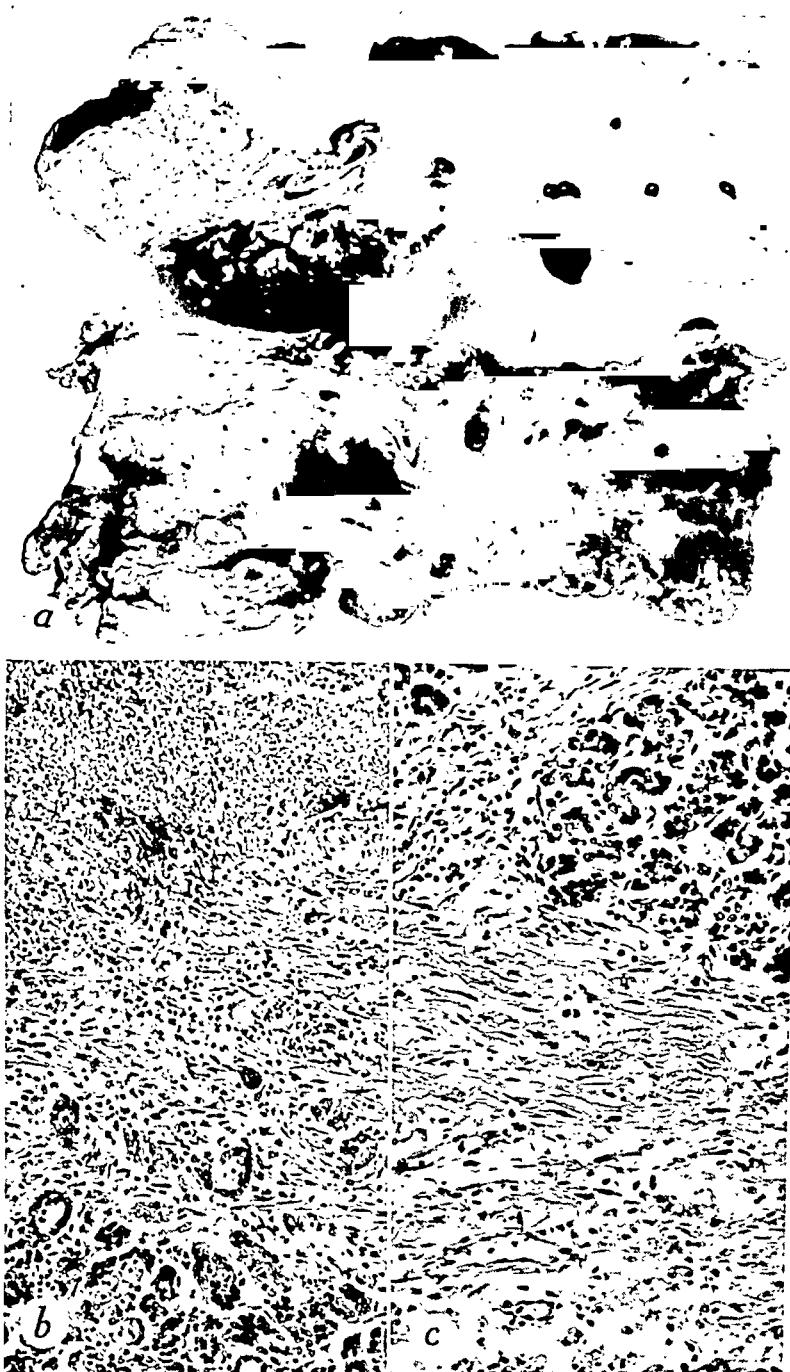


FIG. 1. Pancreas. *a*. Acute hemorrhagic pancreatitis. Note recent hemorrhagic infarction of the body and tail and older inflammatory lesions in the head. *b*. Recent pancreatitis. Note region of necrosis with inflammatory reaction (hematoxylin and eosin  $\times 130$ ). *c*. Chronic pancreatitis. Note older lesion with fibrosis, lymphocytes and phagocytes (hematoxylin and eosin  $\times 135$ ).

cytes in some of the periportal spaces and also in the small bile ducts. The liver cells were large but appeared normal otherwise.

In sections of the gallbladder there was an organizing fibrinous pericholecystitis.

Collections of lymphocytes were observed between the muscle bundles of the wall but the mucosa was not remarkable.

Sections of the small intestine revealed an organizing fibrinous exudate which contained many mononuclear leukocytes on the serosal surface.

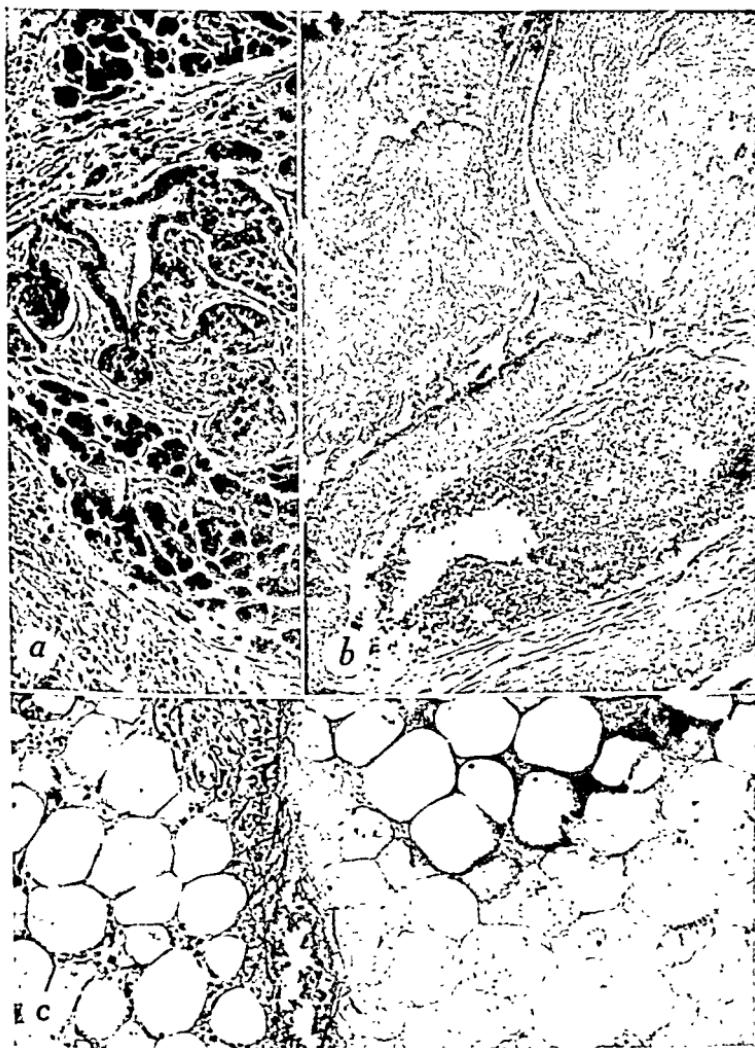


FIG. 2. Pancreatitis. *a.* Metaplasia (squamatization) of epithelium of a small duct (hematoxylin and eosin  $\times 130$ ). *b.* Necrosis of wall of an artery with hemorrhage and thrombosis (hematoxylin and eosin  $\times 60$ ). *c.* Fat necrosis with calcium deposits in omentum (hematoxylin and eosin  $\times 105$ ).

In sections of the kidney the tubular epithelium appeared swollen and hyaline, granular degeneration was observed in a few tubules. An occasional cast of precipitated hemoglobin was present. In the interstitial tissue there was an occasional focus of acidophilic material together with a collection of lymphocytes.

In sections of the mesentery, omentum, parietal peritoneum, perirenal and mediastinal connective tissue there were regions of fat necrosis with considerable amounts of basophilic material which stained like calcium with the von Kossa method (fig. 2c).

The following anatomic diagnoses were made: acute hemorrhagic pancreatitis with disseminated fat necrosis and calcification; general peritonitis (3,000 cc. of fluid); acute cholangitis; choledolithiasis; multiple sessile polyps of the stomach; recent ulcers of the stomach and bilateral hydrothorax (250 cc. on each side) with atelectasis of the lungs.

*Postmortem chemical studies.*—The results of chemical analysis of omental and pancreatic tissues affected by necrosis are given in table 3.

TABLE 3

*Concentration of calcium and phosphorus in pancreatic and omental tissue in a case of acute hemorrhagic pancreatitis with disseminated fat necrosis*

TISSUE	MG. PER 100 GM. OF TISSUE (WET WEIGHT)	
	Calcium	Phosphorus
Head of pancreas (nonhemorrhagic).....	46.7	192.0
Body of pancreas (hemorrhagic).....	131.7	54.2
Omental fat (without necrosis).....	41.9	32.1
Omental fat (area of necrosis).....	261.0	66.0

## COMMENT

*Pathologic aspects.*—In any consideration of the pathogenesis of the pancreatitis in this case it is important to note that the lesions in the head of the pancreas (interlobular fibrosis, collections of lymphocytes) suggested an older process than was found in the body and tail of the gland.

The foregoing observation suggests that this patient had had a number of attacks of pancreatitis or pancreatic necrosis before the final fatal attack. In this last phase of his illness a large artery was eroded with the development of an occluding thrombus and hemorrhagic infarction of the tail and portion of the body of the gland. It is interesting to speculate as to how often a similar chain of events occurs in so-called acute hemorrhagic pancreatitis. Perhaps a large number of patients with the latter disease have a number of previous attacks (relapsing pancreatitis) and fatality ensues only when the inflammatory and digestive process involves vessels which supply a large part of the gland.

From the pathologic features in this case conclusions as to the etiologic factors responsible for the pancreatitis could not be drawn. Although the gallbladder contained stones it showed but little evidence of active inflammation aside from the inflammation of the serosa, which was part of the generalized peritonitis. The cholangitis and pericholangitis also appeared to be recent and were probably a complication of pancreatitis and peritonitis. The

common bile duct contained no stones and was not dilated. The common bile duct and the pancreatic duct were separate up to a point 2 mm. from the orifice; consequently, it would have been impossible for a stone to convert the two ducts into a common channel and allow regurgitation of bile to occur up the pancreatic duct.

The metaplasia (squamatization) of the epithelium of some of the pancreatic ducts which was present in this case has been given an important role in the etiology of pancreatitis by Rich and Duff<sup>1</sup>. One cannot exclude the possibility that it was a significant factor in this case but it is important to point out that squamatization or metaplasia is a fairly common lesion in the absence of pancreatitis and is also frequently absent in cases of pancreatitis. It may be that a combination of factors, namely, infection of the biliary tract and obstruction of the pancreatic ducts, was important in this case and may be important in others.

*General aspects.*—It has been shown, first by Langerhans in 1890 and subsequently by others, that the yellowish areas of fat necrosis observed in cases of acute pancreatitis contain large amounts of calcium soaps which are formed when free fatty acids are liberated by the action of pancreatic lipase on neutral fat<sup>2-5</sup>.

The very low concentration of calcium in the blood serum is of interest. This problem has been studied recently by Edmondson and co-workers<sup>3-5</sup>, who found that in acute pancreatitis with necrosis the concentration of calcium in the serum may become subnormal any time between the second and fifteenth days of the attack, the lowest values on the average being on the sixth day of the attack. Furthermore, they observed that whenever the concentration of calcium in the serum in acute pancreatitis falls below 7 mg., the patient almost invariably dies.

Although the concentration of calcium in the serum in our case ranged between 5.1 and 5.9 mg., yet there was no evidence of tetany and the response to the Chvostek test was negative. The reason for this is not clear. It may be related to the following factors: First, the value for the serum proteins was low, thus allowing sufficient calcium to remain in the physiologically active ionic form. McLean and Hastings<sup>6</sup> have shown that there is a definite relationship between total serum calcium, ionized calcium and serum protein and that at any given level of total serum calcium the diffusible ionic fraction increases as the total serum protein decreases. Second, the serum potassium was also low, so that the ratio of ionic calcium to potassium tended to remain near normal and thus preserve nearly normal neuromuscular irritability. In other words, the stimulating effects on the neuromuscular system of a lowered concentration of calcium was counteracted by the inhibitory effect of a lowered concentration of potassium. It has been assumed by Edmondson and co-

workers<sup>3-5</sup> that in patients with pancreatic necrosis the decreased concentration of calcium in the serum is due chiefly to the combination of calcium with fatty acids liberated by the action of lipase on neutral fat. That this is actually the case has not been proved. Even if this were true, it is hard to understand why in our case enough calcium could not be withdrawn from the skeletal system to maintain a normal concentration of calcium in the blood. The loss of calcium into the ascitic and pleural exudates and by way of aspirations through the gastric and Miller-Abbott tubes possibly contributed also to the low values for serum calcium and potassium in our case.

Edmondson and associates found the concentration of calcium in the normal pancreas to be between 5 and 6 mg. per 100 gm. of pancreas and that in the peripancreatic fat and mesentery to be between 2 and 3 mg. per 100 gm. of tissue. It is therefore apparent that in the case we are reporting the content of calcium in the pancreatic and mesenteric tissues was from 25 to 100 times the normal value.

The reason for the rather low values for serum potassium in our case is not entirely clear. It is probably the result of poor dietary intake, the loss of potassium into the ascitic and pleural exudates and feces and the loss by aspirations from the gastro-intestinal tract. It is felt that in our case insufficient amounts of potassium and calcium were given parenterally to influence materially the blood levels of these constituents.

Ascites is not an uncommon complication of hemorrhagic pancreatitis with disseminated fat necrosis. Bilateral hydrothorax in our experiences has been a rare finding in this disease. It is difficult to ascertain the mechanism for this complication. It may be due to extension of the inflammatory process from the abdominal cavity by way of the lymphatic system<sup>7</sup>.

#### SUMMARY

A clinical, physiochemical and pathologic study has been made in a case of severe acute hemorrhagic pancreatitis resulting in disseminated fat necrosis within and outside the abdominal cavity, generalized peritonitis, ascites, bilateral hydrothorax, diabetes mellitus, hypocalcemia, hypopotassemia and uremia. Interesting is the absence of tetany in the presence of rather low values for serum calcium. Possible explanations for this finding are offered. Chemical analysis revealed that the concentration of calcium in the pancreas and in areas of fat necrosis in the omentum was from 25 to 100 times as high as those which are found in the same tissues not involved by acute pancreatitis.

The evidence in the case just reported tends to support the belief expressed by Edmondson and associates that the concentration of calcium in the serum may be of prognostic value in acute pancreatitis.

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## SCLERODERMA OF THE INTESTINAL TRACT: FIRST REPORT OF A FATAL CASE

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### INTRODUCTION

Scleroderma is no longer considered a purely dermatologic disease. Studies of its many visceral lesions have shown it to be a progressive systemic disease of collagenous tissue. Recently, the number of different organs known to be involved has been increased by observations of lesions of this nature in the gastrointestinal tract<sup>1-5</sup>. While there are numerous studies in the gastroenterologic literature of esophageal scleroderma, none of these concern intestinal scleroderma. The case reported here indicates that intestinal scleroderma is a lesion of gastroenterologic importance since it can in itself lead to a fatal termination.

### CASE HISTORY

Mr. J. F., age 48 years, was first seen in 1940 complaining of stiffness and swelling of many joints, numbness of the hands, and progressive hardening of the skin of his extremities. The skin presented a typical picture of diffuse scleroderma. His face had a mask-like expression. The skin of the extremities was dry, hardened and thickened. All fingers were pointed and their movement was impaired. Roentgenologic examination showed destruction of the ulnar styloid processes, calcification of the synovial membranes of the hamate bones and typical atrophy of the distal phalanges, and forty-two per cent increase in cardiac size. Serum calcium, calcium tolerance and calcium balance were normal.

During the following seven years, the patient was hospitalized seven times because of recurrent painful trophic ulcers of the hands which healed in four to eight weeks with heat, complete bed rest, high caloric diet and local treatment with mild antisepsics. In 1946, because of intractable ulcers, several phalanges were disarticulated.

In June 1941, bilateral cervical and thoracic sympathectomy failed to alter the course of the disease. In 1942, esophageal biopsy specimens had typical sclerodermal changes which explained his progressive dysphagia and the fluoroscopic finding of severe lower esophageal stenosis. Mechanical esophageal dilatation afforded some relief (Case No. 2 of Lindsay, Templeton and Rothman<sup>6</sup>).

In September 1946, the patient developed severe cramping abdominal pain in the left lower quadrant, accompanied by marked constipation. The descending colon was palpable and tender. Because of sharp angulation of the bowel, proctoscopic examination of only 14 cm. of rectum could be accomplished. This rectal mucosa was normal. Because of technical difficulties, barium enema roentgenologic studies

were unsatisfactory. Atropine relieved the pain considerably and the patient was discharged in January 1947 with the provisional diagnosis of scleroderma of the descending colon.

In March 1947, he suddenly developed an upper respiratory infection, followed rapidly by thoracic pain, pulmonary congestion, dyspnea, and progressive abdominal enlargement. Five days after the onset of these symptoms, he was hospitalized in a moribund condition. He had severe dyspnea, generalized cyanosis, a large distended tender abdomen, widespread thoracic rales, and edematous legs. A few hours after admission he passed a bloody stool and shortly thereafter expired.

#### NECROPSY FINDINGS

Because the extra-alimentary lesions of scleroderma have been so thoroughly depicted elsewhere, only the pathologic changes in the alimentary tract will be described here.

#### GROSS EXAMINATION OF ALIMENTARY TRACT

The abdominal cavity contained one liter of thin turbid yellow fluid. From two cm. to the right of the splenic flexure down to the recto-sigmoid junction, the colon was dark red-brown and dilated. The peritoneum over this portion was opaque. It was covered by a fibrinopurulent exudate which was thickest in the mid portion of the descending colon where a small necrotic diverticulum had ulcerated. The mucosa of the externally discolored portion of the colon was dark red, friable and edematous. Along the course of the necrotic bowel were numerous small pseudodiverticula and many ulcers 3 to 5 mm. in diameter, with sharp margins and dirty necrotic floors. Two elongated mucosal ulcers were present in the rectum just below the sharp termination of the sigmoidal gangrene (Fig. 1).

The left coeliac and sigmoidal arteries and veins and their arcadal communications were occluded by propagating bland thrombi.

The esophagus was shorter than normal. Five cm. of the cardiac portion of stomach were intrathoracic. At the cardio-esophageal junction, the lumen of the esophagus was constricted by dense fibrous tissue. The epithelium became progressively thicker and whiter from the mid portion down to the cardia where there was a 2 x 3 cm. clean, stiff-walled ulcer 2 mm. deep. The thickened epithelium was divided into irregular islands by deep linear crypts. The wall of the esophagus paralleled the epithelium in becoming increasingly thicker.

#### HISTOLOGIC EXAMINATION OF ALIMENTARY TRACT

The squamous epithelium of the lower half of the esophagus was about twice as thick as normal. The superficial cells were large and vesicular while the lower layers had prominent intracellular bridges. In the floor of the ulcer



FIG. 1. Photograph of the mucosal surface of the terminal ileum, colon and rectum of this patient, showing the edematous gangrenous segment of bowel and its relatively sharp delineations.

was a small artery completely obliterated by intimal fibrosis and polymorphonuclear leukocytes. The muscularis mucosae in this region was heavily infiltrated by young fibroblasts while above and below this point the muscularis

mucosae was atrophic and penetrated by large collagen bundles. The submucosa nearest the epithelium consisted of extremely dense collagenous tissue.



FIG. 2. Photomicrograph (X20) of the gangrenous sigmoid colon showing the necrotic epithelium, edematous fibrous submucosa, thrombosed veins, and typical atrophy and fibrosis of the circular muscle.

The true muscularis was atrophic and partially replaced and surrounded by this tissue. The arteries had severe intimal fibrosis and many of the small veins

had eccentrically placed myoma-like masses in their walls. The smaller nerve trunks had myxomatous degeneration and varying degrees of replacement by fibrous tissue.

There was a simple incomplete atrophy of all types of gastric mucosal cells. The submucosa was relatively normal. The true muscularis of the stomach had scattered foci of atrophy and fibrosis. Random sections of the small intestine revealed subperitoneal fibrosis, focal severe atrophy and fibrosis of the circular and longitudinal muscles and moderate submucosal fibrosis.

The most marked atrophy and fibrous replacement of smooth muscle was found in the circular muscle of the descending and sigmoid colons (Fig. 2). In places, only small loosely collected bundles of smooth muscle remained between coarse bundles of collagen. The submucosa was greatly thickened even in the non-gangrenous parts of the colon. The fibrotic submucosa of the descending and sigmoid colon was extremely edematous. The mucosa was necrotic or completely missing. Although all tissues in this portion of the colon were infiltrated by polymorphonuclear leukocytes, the greatest collections of these cells were in the walls of severely fibrosed arteries and veins and in lymphatics which these cells occluded. In the areas of ulceration, the typical blood vessel changes in both the arteries and veins were most severe. The subterminal branches of the left colic artery had moderate intimal fibrosis and recent thrombi.

The other organs that contained the characteristic fibrous and vascular lesions of scleroderma were the skin, lungs, heart and kidneys.

#### COMMENT

The intimal fibrosis and edema and venous myomatous proliferation, which were so prominent in this patient, have not been found consistently in all cases of scleroderma. Evidence, however, is accumulating that these lesions are characteristic of this disease and may be involved in the primary pathological process. The vascular lesions played the dominant role in the death of this patient. Most probably, the mucosa of the descending colon was devitalized by the obliterative process in small terminal arterioles with the result that trophic mucosal ulcers formed. With bacterial invasion of these necrotic foci propagating thrombophlebitis, lymphangitis and arteritis developed, progressed and caused the ischemic necrosis of the descending and sigmoid colons. The rapidly occurring fatal peritonitis was undoubtedly the result of the unfortunate presence of pseudodiverticula that ulcerated immediately into the peritoneal cavity. Early recognition of similar situations permitting local intestinal resection and chemotherapy of the intestinal infection may be able to prolong life.

Previous studies<sup>1, 2, 3, 4, 5</sup> have shown that scleroderma of the intestinal tract

is a not uncommon manifestation of this disease and that the diagnosis can be made by fluoroscopy and roentgen films. The present case report emphasizes the inherent danger in this lesion. The possibility that the intestinal form of this disease can cause death must not be overlooked.

#### SUMMARY

A fatal case of scleroderma of the intestinal tract is described briefly clinically and pathologically. The inherently dangerous potentialities of this lesion are emphasized.

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## EDITORIALS

### MANY HEADACHES ARE PRODUCED IN THE MUSCLES OUTSIDE OF THE SKULL

It has long been known that many headaches and especially the nuchal ones are associated with much tension in the muscles. Often a nuchal headache can be rubbed away by a physical therapist. Recently Simons and Wolff (*Studies on headache; mechanisms of chronic post-traumatic headache. Psychosomatic Med.*, 8: 227-242 [July-Aug.] 1946) reported studies of the action currents of the muscles surrounding the skull in persons with headache. With the help of an instrument much like the electro-encephalograph one can tell when a muscle is contracted and active and when it is relaxed. The workers found that feelings of pressure or tightness commonly arise from the sustained contraction of muscles located in the frontal, temporal, occipital or cervical regions.

In some cases the injection of a 1 per cent solution of procaine hydrochloride into the contracted muscle promptly stopped the headache. Some time ago we called attention editorially to the fact that contraction of the muscles of the back of the neck with the resultant distress is an excellent index of the amount of nervous tension in a person's body. The writer of this editorial also once had a remarkable experience showing how a severe headache could result from nervous tension. One morning he awoke with a severe frontal headache worse than he had ever known in his life before. He then remembered that he had just been dreaming that while seated at his desk in the office a fellow physician had telephoned from across the continent asking for a report on a certain patient he had referred. The writer said, "Wait a minute," and started rapidly to hunt through a big pile of histories heaped on his untidy desk. As time passed and he could not find the desired history, he got more and more tense until he woke with the severe headache. By voluntarily relaxing his muscles he was free from pain within a few minutes.

One of the most useful features about the observations of Simons and Wolff is that in many cases of headache the patient can be cheered up and much relieved of anxiety on learning that the seat of his headache is not inside his skull and his brain but outside in the tensed muscles. In some cases there may be some myositis or fibrositis.

W. C. A.

## OBESITY

Every gastroenterologist will find much to enlighten and please him in the excellent review of the subject of obesity by C. F. Gastineau and E. H. Rynearson in the December 1947 number of the *Annals of Internal Medicine*. As these authors point out, a physician is not fair to his obese patients when he does not take pains to point out to them the dangers that reside in their extra burden of fat. Statistical studies show clearly the intensifying effect of obesity on such diseases as hypertension, atherosclerosis, pulmonary emphysema, diabetes, heart disease, cancer, nephritis, cirrhosis of the liver, cholecystitis, arthritis, bad varicose veins, and pulmonary embolism. In the presence of obesity any operation is likely to be dangerous, and pregnancy is fraught with extra dangers.

Between the ages of forty-five and fifty-five the presence of an extra 50 pounds of fat gives the person an extra 50 per cent chance of death in the following year. There are also some bad psychic aspects of obesity. With it there must go a certain amount of childishness, lack of self-control, and lack of self-respect. The very stout woman has lost self-respect and has given up hope of being a sexually attractive person. Often she must be looking forward more or less complacently to the loss of her husband's love and regard and her children's respect.

Highly important is the fact, realized by all physiologists today, but unfortunately not by all physicians, that a gain in weight comes simply from the taking in of excess amounts of food. Whenever a woman eats more than she needs to meet the energy requirements of her body she will have fat to spare, and she then is likely to store it under her skin and elsewhere throughout her body. Stout persons who are always saying, "I don't eat very much," are perhaps thinking of mealtimes. What they seem to forget is that in the kitchen all day they are nibbling or raiding the icebox.

Most physicians still think that the obese person must have something wrong with his or her basal metabolism or with the glands of internal secretion, but actually researches have shown that this is seldom true. Gastineau and Rynearson take up one theory after another which has been proposed to explain obesity and show that there isn't much proof in favor of it. Obesity appears to depend most frequently upon some inherited derangement in the mechanism in the brain which controls appetite. It seems probable that this mechanism resides within the hypothalamus, and that its functions can be considerably modified from the cerebral cortex. That the trouble can arise in the hypothalamus is suggested by the sudden great increase in weight that sometimes

follows that form of encephalitis which injures principally the area at the base of the brain.

One wonders sometimes if the very stout may not represent a variety of the human race, but against this suggestion is the fact that in the Orient where millions teem and food is scarce the farmers and the laborers are thin and spare, and it is only the rich merchant who gets fat.

Gastineau and Rynearson feel that a sane, scientifically planned diet is the only safe and sound treatment. It must be a low calorie diet which is so complete in essentials that it can be lived on indefinitely. It is true, as Ivy and his colleagues have recently shown, that amphetamine and other sympathomimetic amines will in large doses suppress appetite. But even if the giving of such drugs proves to be safe, their use in the reduction of weight is likely to be inadvisable because they divert the patient's mind from the fact that the essential feature of the treatment must always be the diet. A woman is much more likely to cheat on the diet if she thinks she can cover up her sins by taking more of the medicine.

No one should beg a stout woman to reduce, and no one should watch over her in an effort to prevent cheating. "It's her funeral." For her own salvation and future she must want very much to reduce and then to stay thin. She must want this so much that she is ready to suffer for it and to struggle on alone. Before she starts on this diet she should be made to understand fully that she must stick to it probably for the rest of her days. There is no use wasting time with the woman who wants only an "eighteen day Hollywood diet." Even if she takes off a lot of fat she will probably put it right back on again as soon as her enthusiasm wanes.

W. C. A.

## COMMENT

### SOME RECENT REVIEWS OF THE LITERATURE ON VAGOTOMY

In the October 23, 1947, number of the *New England Journal of Medicine*, William R. Moses presented an excellent critique of vagotomy. First he reviewed the results of the treatment of ulcer as published by many authors. Interesting was the study of Krarub who, after watching the results of medical treatment for five years in the cases of 665 patients with ulcer, concluded that only 29 per cent had a good recovery, 36 per cent were improved, and 35 per cent had a poor result.

Moses doubted if vagotomy needs ever to be performed for gastric ulcer because the results of resection in such cases are so good that there is little need for doing anything more; jejunal ulcers almost never come as they do in cases of duodenal ulcer.

Moses was not satisfied that vagotomy has yet been shown to correct the faults of function which lead to the production of ulcer. He might have added that it hasn't yet been proved that vagotomy will in most cases prevent the formation of a jejunal ulcer. Certainly reports are coming in of jejunal ulcers that have appeared after vagotomy. Moses commented on obstruction at the cardia which in a few cases can be very troublesome after vagotomy.

The impression gained by Moses and others is that vagotomy might be used in cases of jejunal ulcer after subtotal gastrectomy if it will only save the patient from the risk of the big and serious operation of taking out the ulcer and resecting some more stomach. Moses thought that vagotomy might also be done in cases of penetration of a duodenal ulcer into the head of the pancreas. This is questionable because in this type of case, partial gastric resection usually gives excellent and lasting results. It is also highly desirable in such cases that all gastric juice be shut off from the duodenum.

A good bibliography of 114 titles accompanies Moses' article.

W. C. A.

## AN ILEAC STOMA COVERED WITH A SKIN GRAFT

No surgeon likes to make an ileac stoma in a case of chronic ulcerative colitis; it is not a pleasant thing for the patient, but at times there is no other sensible way out of his dilemma. Perhaps the ulcerative colitis is severe and intractable, or there is diffuse polypoid disease which will sooner or later give rise to carcinomas, or life is threatened by colonic strictures, perirectal abscesses, massive hemorrhages, subacute perforations, or definite malignant lesions. In such cases an ileac stoma has to be made and often later the non-functioning colon has to be removed.

One of the most distressing of the complications which follow creation of an ileac stoma is the excoriation of the skin by the contents of the bowel. This ulceration is not only painful but weakens the patient and is hard to treat. A number of appliances have been tried out, some of them cemented to the skin, and a number of ointments have been used to protect the skin but none has ever been entirely satisfactory. The main difficulty with the ordinary ileac stoma is that a sufficient length of bowel is not left sticking out to deliver the contents of the gut into the rubber bag made to receive them.

In 1941 Dragstedt, Dack and Kirsner (*Ann. Surg.*, 114: 653-661 [Oct.] 1941) found that they could cover an exteriorized segment of ileum with a skin graft and leave it sticking out of the abdomen like a spigot. They found this worked well. Recently Black and Thomas (*Proc. Staff Meet., Mayo Clin.*, 22: 508-511 [Oct. 12] 1947) reported having made four such skin-grafted ileac stomas. In each case there was virtually a complete take of the skin graft on the serous coat of the bowel, and in each case the presence of the spigot made life easily bearable for the patient. In none of the cases did there follow immediately the profound upset in the balance of fluids and electrolytes which has so commonly been seen after the performance of the usual ileostomy.

Bargen remarked in the discussion on this last paper that in his opinion this new operation constitutes the greatest single advance in the surgical care of patients with disabling ulcerative colitis. The stoma is so much easier to manage and the skin does not get excoriated. It would appear now that the old type of stoma should never again be made.

W. C. A.

## IS URTICARIA OFTEN PRODUCED BY AMEBIASIS?

Giordano believed that in some instances urticaria can be explained by the presence in the bowel of endameba histolytica. In order to see if this is true one hundred cases were studied in which urticaria was a prominent complaint. In this group of patients extensive studies of stools revealed only four cases of amebiasis. Eradication of the amebiasis did not relieve the urticaria in any instance.

In a study of 790 patients with amebiasis, urticaria was present in only 36 cases. In none of these 36 could the urticaria be related to the amebiasis, and in none was there evidence that amebacidal therapy affected the urticaria.

Accordingly, the impression remains that there is no causal relation between amebiasis and urticaria.

GORDON McHARDY

## BOOK REVIEW

TUMORES DE LOS ISLOTES DE LANGERHANS HIPERINSULINISMO. *By Rodolf Lopez Kruger.* Stanley, Santiago, Chile, 1946.

This is a fine monograph on tumors of the Islets of Langerhans as they were observed by Lopez Kruger when he was a Fellow at the Mayo Clinic in the years from 1942 to 1945. The monograph is well-written and well-documented. As Lopez Kruger says, at the Mayo Clinic they have found only 44 tumors of the islets in 10,314 autopsies.

Many of these tumors apparently do not produce symptoms, and yet they look exactly like those that do give trouble. True hyperinsulinism due to one of these tumors is a very rare disease.

Out of 216 tumors that produced some hyperinsulinism 153 were benign adenomas. Malignant tumors of the islets with metastasis have been seen only seventeen times so far.

A HISTORY OF SCIENTIFIC ENGLISH, THE STORY OF ITS EVOLUTION BASED ON A STUDY OF BIOMEDICAL TERMINOLOGY. *By Edmund Andrews, M.D.* Richard Smith, New York, 1947. 342 pp.

Here's one of the most delightful and instructive books that the reviewer has run onto in years. An able surgeon, Andrews was also a scholar who had an unusually good working knowledge of Latin and Greek besides his knowledge of French, German, and Polynesian. He even found time to write a dictionary of Tahitian. It's sad to think that he had to die at the age of forty-eight.

The book is so full of interesting facts that one doesn't know where to begin. For instance, the word "pluck," meaning courage, referred to the viscera of fowls plucked out in preparation for the table. Obviously, then, the word means the same as guts. One reads such curious things as that our word syringe came from a word meaning a flute in the Cretan language. It also meant a rectal fistula. Interestingly, many of our words for drugs came from the ancient language of Crete.

A point which Andrews makes again and again is that since physicians have always used Greek and Latin in their terminology and since they have always been rather conservative, medical literature is a museum of philologic antiquities. The word medicus is not even Latin: it came from the old Oscan or Sabine speech. It meant an intermediary—perhaps between God and man.

The word Hippocrates shows that the father of medicine came from a race of horse tamers. The root of the word therapeutics originally meant in Homer's speech a junior companion in arms. Later it meant a nurse or an orderly in a clinic. One meaning of the root was service. Our Aesculapius came from a word meaning a snake, and we know that the early temples of

healing often kept pythons about the place. As everyone knows there is a snake twined around the staff of Aesculapius. The original word for glass was hyalos and from that we get our medical term hyaline.

Interesting is the derivation of the word for "work." It meant originally to be tired and worn out! The word pharmacy came from a root similar to that which produced our word "farm" and "barn." Originally it had a meaning of poison or of the paints used by an artist. The word meconium meant not only the first bowel movement of a baby but opium, which looks like it. Diabetes originally meant a pair of compasses. Amnion was a sacrificial bowl. The prostate in Greek meant a protector or patron. Rather suggestive is the fact that the word epidemia meant the annual progress of a sovereign through his domains, collecting taxes! Evidently it was not looked on as a blessing. A curious ending is "itis" meaning nowadays, disease. Originally its meaning was "of the." For instance in Hippocratic times the word "arthritis" was followed by "nosos" which together meant disease of a joint. Finally the "nosos" was left off. The grammarian is particularly scandalized when he sees us adding to the genitive ending "itis" a plural ending so as to make a word like gastritides. But as Andrews says, there isn't much the grammarian can do about the things that outrage his sense of proprieties. He knows that no matter how ungrammatical a term is it will stick if it is useful.

Curiously, the word "carotid" comes from a Greek work meaning to put to sleep. Apparently it was early known that pressure on the two carotid arteries would produce unconsciousness.

It is particularly interesting to hear Andrews say that the old story that the books in the huge library of Alexandria were used to heat the public baths is not quite true. He says that the works on science, natural history, and medicine were specifically exempted from the holocaust and were copied and scattered all over the Moslem world. They created a thirst for knowledge that was not satisfied until all of Greek learning had been translated into the Arabic tongue. Later it was translated from the Arabic into Latin and that was part of the process that brought back learning to Europe. A number of the early medical classics were first translated into Hebrew or Aramaic and then into Arabic.

The word alkali comes from kali or ashes, and the word alcohol originally meant a triturate. Aniline comes from the Arabic "anal" meaning a pigment. According to Andrews, the word chemistry comes from a Greek work chumos which gave us the word chyme. The word sugar came into Europe from India by way of Arabia. The Hindu word was "sakkara" which we now use in the term "saccharine." The word feces came from "faex" which was the Roman name for the lees of wine. In Persian this was called "durd" which later changed to an English four-letter word and also to the word "tartar." Rather

appropriate is the descent of the word malade from an older form, malapte meaning badly fitting. The mentally sick person today fits badly into his environment. The word bastard came from words which meant son-of-a-mattress. In German he's called a son-of-a-bench.

The word ill is a relic of Norse. The Saxon word was seocnisce or our sickness. In the earliest medical pamphlet in Saxon there is a mention of "half a headache" or migraine. The word courtesan meant a man or woman around the court, which doesn't speak highly for the morals of the court. Similarly the word pimp was originally French pimper which means to dress stylishly—probably our "primp."

Andrews shows that again and again certain words which were originally so perfectly proper that they are to be found in the earliest English Bible, became "dirty," and then new ones had to be found.

This is a book to have by the side of the bed for reading during the last half hour of the day.

A TEXTBOOK OF DIETETICS, CLINICAL GUIDE TO DIET THERAPY. By L. S. P. Davidson, and I. A. Anderson. Hoeber, New York, 1947, pp. 517, second edition, \$6.00.

This is an attractive book crammed with information. Doctor Davidson was formerly Regius professor of medicine in the University of Aberdeen, and Doctor Anderson is lecturer in clinical chemistry in the University of Aberdeen and formerly Advisor in Nutrition to the War Office.

BIOLUMINESCENCE, ANNALS OF THE NEW YORK ACADEMY OF SCIENCES. By E. Newton Harvey, Rupert S. Anderson, John B. Buck, Orrin M. Chase, Henry Iring and Frank H. Johnson. Vol. 49, article 3, pages 327 to 482.

One of the most remarkable phenomena of nature is the luminescence shown by a number of fishes and flies and worms. As everyone knows the outstanding research worker in this field has been E. Newton Harvey. Years ago he worked out much of the chemistry of the production of the light and the relation between luciferin and luciferase, the ferment. All those many physicians who are interested also in biologic processes, anywhere in nature, will be much interested in this splendid little monograph.

MY POLIO PAST. By Noreen Linduska. Pellegrini & Cudahy, Chicago, 1916.

One of the best things a physician can do in order to learn about the mental processes of patients with serious diseases is to read books which they write about their experiences. One can learn so much about their psychology, about the things that bother them, the things in the doctor's office and the hospital which frighten them or outrage them, and the things which we of the medical profession do that reassure them and make them glad. In this book, Miss Linduska, who is a keen, wideawake advertising writer, full of ideas, tells about her experience with first,

bulbar polio and a few weeks later generalized muscular paralysis. She gives a vivid description of the distress she went through as the muscles in her larynx and throat failed to function. She tells vividly what a patient feels when treated with the Kenney packs and she tells much about the life of the "chronic" patients in a big hospital. The book is very sprightly and well-written.

**DIFFERENTIAL DIAGNOSIS OF JAUNDICE.** *By Leon Schiff, M.D.* The Year Book Publishers, Inc., Chicago, 1946.

In these days when the interest in jaundice and hepatitis is greater than ever and when tests are being devised which help in the differentiation of the several types of jaundice, there is great need for good books on the subject. Schiff's book is one of the most thorough and satisfactory that we have seen. It is crammed with valuable material and information throughout its 313 pages. It is well written and well illustrated.

The seven main parts of the book are on Characteristics and Classifications, Parenchymal Jaundice, Neoplastic Jaundice, Calculous Jaundice, Retention Jaundice, Clinical and Laboratory Aids in Differential Diagnosis and an Appendix covering laboratory methods. Dr. Samuel Rapoport wrote the section on the Jaundice of the Newborn.

This book is so good all the way through that it is hard to pick out any one chapter for special praise. It is a book that ought to be on the shelves of every gastro-enterologist.

**FORTY YEARS OF SILENCE.** *By Clifford A. Brown.* Marshall Jones Company, Francestown, New Hampshire, 1946. pp. 80.

As has already been noted in other reviews, one of the best things a physician can do while learning to understand the mental processes of his patients is to read accounts of their illnesses written by them. This book is a fine, interesting story of a man who has been deaf for forty years.

One is reminded of what Huxley once wrote to Darwin. He said he was much annoyed because he was growing deaf, he was even more annoyed because people were noticing it, and he was still more annoyed because he was annoyed when people noticed it.

# ABSTRACTS OF CURRENT LITERATURE

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## MOUTH AND ESOPHAGUS

WHEELER, D. Diverticula of the foregut.  
*Radiol.*, 49: 476 (Oct.) 1947.

The author describes diverticula of the different portions of the foregut and shows roentgenograms of his cases. With the exception of the diverticula at the pharyngeal-oesophageal junction, there are usually only incidental findings. The oesophageal-pharyngeal diverticula produce definite symptoms, the others are practically asymptomatic. Diverticula of the lower oesophagus are important when instrumentation is contemplated. Because diverticula are so readily demonstrated by an X-ray examination, their significance, except for the oesophageal-pharyngeal type, has been greatly exaggerated.

FRANZ J. LUST.

## STOMACH

SEGAL, H. L., WATSON, J. S., AND STEINHAUSEN, T. B. Difficulties in the diagnosis and treatment of lesions of the pyloric antrum. *N. Y. State J. Med.*, 47: 2292 (Nov.) 1947.

There are several conditions which may

cause confusing shadows in X-rays of the pyloric antrum. These include normal variations in size of rugae, pylorospasm, gastritis, benign pyloric hypertrophy, gastric ulcer, carcinoma, benign tumors, lymphosarcoma, syphilis, and tuberculosis. For practical purposes, the differential diagnosis lies between malignancy and benign ulcer. Repeated X-ray, laboratory and gastroscopic studies must be carried out in case of doubt, especially if symptoms persist. Exploratory laparotomy is indicated if the diagnosis cannot be reached within a reasonable time. A normal blood count, and the absence of occult blood in the stool do not rule out carcinoma. Any narrowing of the lumen in the X-ray after sodium amyta suggests a hypertrophic or infiltrative lesion, rather than a spasm. Patients with hypertrophic gastritis must be kept under constant observation. Surgery is not indicated as long as the symptoms respond to a medical regimen even in the presence of abnormal X-rays. A benign lesion high up in the stomach may cause secondary pylorospasm or spasm of the duodenal cap. Nine illustrative cases are reported.

PHILIP LEVITSKY.

WELCH, C. E. Carcinoma of the stomach. *Surg. Clinics N. Am.*, 1100 (Oct.) 1947.

The diagnosis of carcinoma of the stomach has not shown any general significant improvement in recent years, mainly because patients are not coming to physicians and clinics for diagnosis earlier than they did in the past. A careful history, stomach X-rays, gastroscopy, and examination of the gastric contents for malignant cells are the most important diagnostic procedures. The last mentioned procedure is of considerable value when positive, but does not rule out cancer when negative.

Surgical therapy, however, has improved in recent years, particularly with reference to a lowering of mortality rates in gastric resection. Mortality has been lowered from 26 per cent in 1937-1941 to 11 per cent in 1941-1946.

Prognosis is based on microscopic pathologic findings. Carcinoma in situ and polypoid cancer offer an excellent prognosis, whereas that for adenocarcinoma and colloid adenocarcinoma is only fair. Signet cell and undifferentiated carcinoma are attended by a poor prognosis, particularly if associated with lymph node metastases or fixation of the stomach to other viscera.

FRANK G. VAL DEZ.

FRIEDRICH, L. Der Platz der Gastroskopie in der Magendiagnostik [The Place of Gastroscopy in Diagnosis of Gastric Lesions]. *Gastroenterologia*, 72: 216, (1947).

Gastroscopic examination is indicated in all patients suffering from a gastric disorder in whom X-ray examination gives doubtful results or findings which are not in accord with the results of other investigations. The gastroscopic findings should be correlated with the data obtained by other methods of examination. Apart from cases with gastric symptoms with negative X-ray findings, the procedure should be used to assess the healing of a gastric ulcer and to elucidate postoperative gastric symptoms. In the differential diagnosis between ulcer and cancer, gastroscopy cannot decide with certainty but rather gives a clue as to the operability of cancer if present. Patients with unexplained gastrointestinal bleeding and

those who apparently have a gastric neurosis should be examined gastroscopically for evidence of gastritis.

CHARLES A. FLOOD.

SCHOEN, A. M. AND GRISWOLD, R. A. The effect of vagotomy on human gastric function. A preliminary report. *Ann. Surg.*, 126: 655 (Nov.) 1947.

The authors studied gastric function in 30 patients who received vagotomy (21 supra-diaphragmatic and 9 subdiaphragmatic surgical approach). Phenol red was introduced into the stomach to indicate the extent of gastric secretion (by change in concentration of the indicator) and of gastric emptying (by change in total quantity of the indicator). The average secretory rate in response to the insulin test (15 units intravenously) was 3.25 cc. preoperatively and 2.09 cc. per minute postoperatively.

LEMUEL C. McGEE.

HARDT, L. L. AND BRODT, L. P. Aluminum hydroxide and magnesium trisilicate plus mucin in treatment of peptic ulcer. *Arch. Surg.*, 55: 584 (Nov.) 1947.

When mucin is added to a mixture of aluminum hydroxide and magnesium trisilicate and taken orally a coating of the gastric mucosa is noted, the pepsin activity and acidity of the gastric juice are lowered and the emptying time of the stomach for this substance is delayed. These actions of the mixture are considered distinct advantages in the treatment of peptic ulcer. The coating action and emptying time were observed gastroscopically and roentgenologically. Peptic activity was tested on the muscle of a frog's leg, while the acidity of the gastric juice was tested after administering 0.5 mg of histamine phosphate.

C. WILMER WIRTS, JR.

### BOWEL

WILLIAMS, H. Appendicitis in the young child. *Brit. Med. J.*, 4531: 730 (Nov.) 1947.

Among 1,487 children under the age of 14 years treated for acute appendicitis, 42 were under the age of 3 years. In this latter group, an acute uncomplicated appendicitis

was found in 6, a gangrenous, perforated appendix with local peritonitis in 21, and a general peritonitis in 15 patients. The author directs attention to the long time interval from the onset of symptoms to the diagnosis, and the more rapid progression of the inflammatory process to gangrene and perforation. The small immature omentum also fails to assist in sealing off the appendix effectively from the general peritoneal cavity. Early diagnosis depends upon an awareness of the possible presence of appendicitis and a careful history and clinical examination.

All patients were subjected to operation as early as possible. The appendix was removed in all cases; drainage was established in the presence of a mass or peritonitis. Sulfonamides were given either by mouth or intravenously in one-third of the group. There were 8 deaths among the 42 patients. The most important factor in mortality was the presence of general peritonitis.

JOSEPH B. KIRSNER.

DOUB, H. P. Malignant tumors of the small intestine. *Radiol.*, 49: 441 (Oct.) 1947.

The recognition of malignant tumors of the small intestine depends upon a thorough evaluation of the clinical features, including laboratory studies, and especially upon a careful roentgen study. Much of the improvement in the recognition of these tumors during the past decade has resulted from the more widespread use of serial study of the small bowel. The highest percentage of malignant neoplasms of the small bowel are adenocarcinomas. Lymphosarcomas are second in occurrence and carcinoid tumors a poor third. Grossly the tumors are of two types: constricting and fungating, or polypoid. The constricting type produces mechanical obstruction by narrowing the intestinal lumen, while with the polypoid type, obstruction is due to the bulk of the tumor or to intussusception. The clinical picture is usually one of a progressive loss of weight and strength and varying degrees of anemia. Pain is a prominent symptom. A change of bowel habit is usually present and this may go on to an acute obstruction which brings the patient

to seek relief. A palpable tumor is an important and significant finding. Distension is often present. Unusual peristaltic action is common.

The roentgen picture is one which is common to the neoplasms of the gastrointestinal tract. The abnormal findings may consist of an area of narrowing of the lumen of the bowel and dilatation proximal to it. Marginal or central filling defects may also be present, with obliteration of the mucosal markings in the involved area. Doub's series of 52 malignant tumors of the small intestine includes 21 carcinomas of the duodenum and 1 lymphosarcoma. In the periampullary type, jaundice, often of an intermittent character, is a prominent feature. Pain is the outstanding symptom. In about 50 per cent of the cases, a palpable tumor is present. Secondary duodenal displacement, peristaltic reversal, and gastric retention is found. The series includes 14 primary malignant tumors of the jejunum. Lymphosarcoma occurred eight times, mostly in the ileum. Carcinoid or argentaffin tumors were found in four instances.

FRANZ J. LUST.

ALLEN, A. W. Carcinoma of the large intestine. *Surg. Clinics N. Am.*, 1018 (Oct.) 1947.

Since the development of better bowel preparation, resection with primary anastomosis has become the method of choice, thereby reducing the morbidity. Exteriorization, preliminary cecostomy, or transverse colostomy are rarely used except in complete obstruction due to carcinoma and in large obstructing inflammatory lesions. It is more important to accomplish one-stage resections in the transverse colon than in any other segment of the large intestine because of the variations of the blood supply to this region. Five illustrative case histories are reviewed in detail from the clinical, pathological and operative viewpoints.

FRANK G. VAL DEZ.

OSGOOD, E. C. The role of the radiologist in the management of patients with intestinal obstruction, with special reference to the use of the Miller-Abbott tube. *Radiol.*, 49: 529 (Nov.) 1947.

A detailed description of the use of the Miller-Abbott tube in intestinal obstruction is given. The technique described is comparatively simple. The advantage of the use of the tube is that it often converts an emergency into an elective procedure. The absence of the high degree of distention of the bowels simplifies the surgical procedure. In cases of mechanical obstruction, the tube may be considered as a useful adjunct. It has proved in reflux ileus to be a therapeutic in itself, since surgical enterostomy is generally conceded to be valueless and sole reliance must be placed on non-surgical decompression. In such cases the results with the tube have been excellent.

There are few contraindications to the use of the Miller-Abbott tube. It must not be used in persons known to have or suspected of having strangulation or gangrene of the bowel if operation is thus delayed. Its use is also contraindicated in external hernias since some contain strangulated intestinal loops. In cases of obstruction of the large bowel, there is an increase in the tonus of the terminal ileum which makes uncertain and delays the entry of the tip of the tube into the cecum. Besides, the cecal contents are ordinarily too grumous for aspiration through the tube.

As repeated fluoroscopy and roentgenographs are necessary to determine the site of the tube and the type of the obstruction, the Miller-Abbot tube is best used under the supervision of a radiologist.

FRANZ J. LUST.

JAMESON, J. W. AND MULLINS, C. R. Carcinoma of the colon and rectum. *New Engl. J. Med.*, 237: 699 (Nov.) 1947.

This report is based on 71 cases of carcinoma of the colon and rectum in a 10-year period from a small community of 28,000 population. In 14 cases the carcinoma involved the ascending colon; in 7, the transverse colon; in 17, the descending colon and sigmoid; and in the 33 cases, the rectum was the site of carcinoma. Forty-nine cases were resectable, and 45 were resected for cure with one death. The 3-year survival rate was 46 per cent. Of 18 patients seen five or more years ago, 11 were treated for possible cure, and 7 were treated palliatively.

Two of the patients treated survived 5 years or longer.

The authors describe the treatment in detail, and state that while the results leave much to be desired, they are not wholly discouraging.

ANTHONY M. KASICH.

MAHORNER, H. AND KISNER, W. Diverticula of the duodenum and jejunum. *Surg. Gyn. Obs.*, 85: 607 (Nov.) 1947.

The purpose of this paper is threefold: (1) to present the known facts concerning duodenal and jejunal diverticula, (2) to evaluate the surgical significance of these diverticula, and (3) to discuss the technical features involved in operations for these lesions and report a new technical procedure which insures overlooking any duodenal diverticulum at the operating table. The patient may be cured by surgery designed to obviate these lesions either by inversion into the intestinal canal or by actual removal. The new procedure discussed insures the discovery of hidden diverticula at the time of operation by inflating the duodenum with air. Six cases of diverticula of the duodenum and jejunum are reported. All patients were relieved of symptoms by use of this technique.

FRANCIS D. MURPHY.

BAUMGARTNER, C. J. Survey of intestinal obstruction. *Arch. Surg.*, 55: 607 (Nov.) 1947.

Among 1,107 proved cases of acute intestinal obstruction, adhesive bands was the commonest cause. Thirty-one were classed as early post-operative cases, and 328 as late post-operative cases. The youngest patient was four days old and the eldest 86 years. There were 139 treated by suction alone and 189 were operated on. The duration of obstruction was found to have nothing to do with the degree of obstruction present; a twelve-hour obstruction was often gangrenous while a three-day obstruction might be perfectly harmless. Eight deaths in the group with obstruction due to bands and adhesions were attributed to delay in recognizing the strangulating lesion; each of these patients was treated with siphonage for from two to seven days before surgical interven-

tion. It is emphasized that undue reliance should not be placed on indwelling siphonage, all surgically treated patients should receive blood or plasma or both, and massive doses of penicillin should be employed prophylactically routinely.

C. WILMER WIRTS, JR.

**LAZARUS, J. A. AND MARKS, M. S.** Benign intestinal tumors of vascular origin. *Surgery*, 22: 766 (Nov.) 1947.

Benign intestinal tumors of vascular origin are quite rare. They have been described pathologically as nevus, angioma, cavernous angioma, capillary hemangioma, varicosities and cavernous phlebectasis. The lesion is most frequent in the small intestine, but may occur anywhere in the intestinal tract. The most common symptom is bleeding which may be massive at onset or persistent for many months. Diagnosis is difficult. Treatment may include resection of tumor, resection of bowel, local cauterization, and roentgen therapy. The prognosis is poor, especially for multiple lesions. The disease should be considered in cases of severe intestinal bleeding where a lesion can not be demonstrated. Exploration will usually be required.

J. DUFFY HANCOCK.

**STROHL, E. L.** Acute appendicitis. An analysis of eight hundred and seventy-eight cases at St. Luke's Hospital, Chicago.

*Arch. Surg.*, 55: 530 (Nov.) 1947.

In a series of 878 cases of acute appendicitis, 97 were accompanied with perforation and peritonitis and 56 with abscess. The overall mortality rate was 1.48 per cent. Eleven of a total of 13 patients died as a direct result of progression of the appendical infection or of specific complications. Delay in operation continued as a major factor in death in the cases of acute disease with perforation. The average time which elapsed between onset of symptoms and admission to the hospital was 67 hours.

C. WILMER WIRTS, JR.

#### LIVER AND GALL BLADDER

**ZONDEK, B. AND BROMBERG, Y. M.** Infectious hepatitis in pregnancy. *J. Mt. Sinai Hosp., N. Y.*, 9: 222 (Sept.-Oct.) 1947.

A clinical study of infectious hepatitis was made in 29 cases observed among 3,382 pregnant women—an incidence of 0.85 per cent. The patients were divided into 3 groups according to clinical severity. The smallest group consisted of 2 mild cases who showed transitory bilirubinuria but no clinically apparent jaundice. The largest group (18 patients) had a moderately severe hepatitis. The remaining 9 cases (31%) had severe hepatitis with a tendency to acute atrophy of the liver, thus emphasizing the frequency of this severe form of hepatitis in pregnant women. Five patients of this last group died from acute hepatic atrophy. In 2 patients, chronic hepatitis resulted from infectious jaundice during pregnancy. Twenty-one patients showed no signs of liver function impairment when examined 3 to 6 months after recovery. No functional hepatic impairment was found in 3 women, who became pregnant again. Inadequate estrone inactivation (positive estrone clearance test) is one of the tests of severe liver impairment. An investigation of the effect of infectious hepatitis on the course of pregnancy showed that hemorrhage was exceptionally rare and was observed in only 2 cases shortly before death. Twenty-one patients (72%) recovered completely from infectious hepatitis during pregnancy.

Premature deliveries are frequent in the severe form of hepatitis. Labor proceeded rapidly throughout all the stages. Agalactia and hypogalactia are common in those delivered during the course or shortly after recovery from infectious hepatitis. The fetus was never affected by the disease of the jaundiced mother. Pregnancy is the decisive factor contributing to the severity of hepatitis. All 5 fatal cases and most of the severe cases were observed during the late second half of pregnancy. All patients with the severe form of hepatitis were undernourished, their daily diet being particularly low in proteins and in various factors of vitamin B complex. Excessive vomiting and the presence of the height of a general epidemic lend to the severity and mortality. Therapeutic interruption of pregnancy should be discouraged in the interest of both mother and fetus.

ALBERT CORNELL.

LIPP, W. F., LENZNER, A. R., AND AARON, A. H. The value of symptoms and physical signs in the differential diagnosis of jaundice. *N. Y. State J. Med.*, 47: 2453 (Nov.) 1947.

The differential diagnosis between intrahepatic and extrahepatic jaundice depends largely on the clinical evaluation and not on any specific laboratory procedure. An analysis of 412 cases of jaundice yielded many clinical features. Intrahepatic jaundice occurred in patients under 40 years of age in 75 per cent of cases, and 73 per cent of jaundiced patients over 50 years had some form of extrahepatic disease. In cirrhosis of the liver and carcinoma of the pancreas the ratio of men to women was 2:1, whereas in dystrophy and common duct stone, the ratio was reversed. Pain was a much more prominent symptom in extrahepatic jaundice. Chills suggest common duct stone or infectious hepatitis. Emesis and pain are in keeping with common duct stone, but emesis without pain favors hepatitis, or dystrophy. Marked weight loss was seen in 15 per cent of patients with common duct stone, and in an equal proportion of those with cirrhosis. The liver was enlarged in most cases, except in some of the dystrophies and cirrhoses. Tenderness was elicited more frequently in hepatitis and common duct stone. A palpable spleen favors intrahepatic jaundice. The presence of a palpable gallbladder points to extrahepatic disease. Ascites is of no great differential value. Angiomata were present in 35 per cent of patients with cirrhosis. The color of the stool merely indicated the degree of obstruction, which was greater in extrahepatic disease.

PHILIP LEVITSKY.

MIRIZZI, PABLO L. Functional disturbances of the choledochus and immediate cholangiography. *Prensa méd. argent.*, 34: 2273 (Nov.) 1947.

The author diagnoses biliary dyskinesia only when lipiodol goes into the duct of Wirsung during immediate cholangiography. He calls the syndrome characterized by stasis and marked dilatation of the biliary tract "anatomofunctional disturbance of the hepatic duct". In such cases, immediate cholangiography shows a normal chole-

dochus, and there is jaundice that subsides with biliary drainage and rest. This syndrome can be due to adhesions, stone in the gallbladder neck, abnormal vessels, etc.

The author considers immediate cholangiography the most important help the surgeon has in biliary surgery, for it shows not only anatomic but also functional disturbances. It is of great value in diagnosing functional disturbances resulting in gallbladder stasis, in cholelithiasis, and in postcholecystectomy syndrome. In gallbladder stasis it aids in the diagnosis of an incomplete obstruction of the cystic duct or of a disturbance of the sphincter of Oddi. In 10 per cent of cholelithiasis cases, we can see a functional disorder of the distal end of the choledochus; the bile flows intermittently, the lipiodol evacuation is delayed, the choledochus presents increased peristalsis, and sometimes there is back flow into the Wirsung duct. The author advises a cystoduodenostomy in these cases, and claims this operation has reduced the incidence of the postcholecystectomy syndrome from 10 to 2 per cent in his hands. He has operated on 44 cases of postcholecystectomy syndrome and has always found a functional disorder in these cases as shown by an immediate cholangiography. The author never uses sphincterotomy or a T-tube in these cases but prefers to perform a choledochoduodenostomy.

ALOYSIOS FARIA.

PRISBRAM, B. O. C. The method for dissolution of common duct stones remaining after operation. *Surgery*, 22: 806 (Nov.) 1947.

Stones are left behind in 16-25 per cent of patients operated upon for choledocholithiasis. Such stones may be in the intrahepatic ducts, but more usually are lodged in the ampulla. Retroduodenal or transduodenal exposure will reveal many of the latter but these procedures are accompanied by too great an increase in mortality. A subcostal incision is recommended; the common duct should be explored through an incision in the duct half way between its junction with the cystic duct and its communications with the duodenum (and not through the split cystic duct); aspiration of the common duct before exploration is of value. Accessible stones

should be removed and a sound passed into the duodenum if it can be done without force. If obstruction is encountered, a double-barrelled catheter rather than a T-tube is passed down to that level. The opening in the common duct is made water tight. On the fifth postoperative day a cholangiogram is made, using 15 to 20 cc. of warm lipiodol in oily solution. If stones are present, the bile is aspirated from the fasting patient, and ether is injected drop by drop until the patient feels pressure. The ether is then aspirated and reinjected several times. Following this, 5 to 10 cc. of warm olive oil are injected and the tube clamped for several hours. The procedure may be repeated several times a day. One to six weeks may be required for successful dissolution of the calculi. The method is safe and effective with the above technique.

J. DUFFY HANCOCK.

HOFFMAN, J. AND LISA, J. R. Significance of clinical findings in cirrhosis of the liver. A study of 93 autopsied cases. Am. J. Med. Sci., 214: 525 (Nov.) 1947.

The authors compared the clinical and pathologic findings in two groups of cases of fatal Laennec cirrhosis in the New York City Hospital. Group 1 consisted of 37 cases dying between 1920 and 1934, and group 2, of 56 cases, between 1935 and 1945. The most significant difference was in the occurrence of hemorrhage: 30 per cent in group 1 and 52 per cent in group 2. This finding was substantiated by anatomic evidence of collateral circulation in 35 per cent of patients in group 1 and 66 per cent in group 2. Nutrition was better in the latter group. Ascites was the most common symptom in both groups (58%). Where liver function tests were used the cholesterol-ester fractionation appeared to be more sensitive (altered in 96 per cent of cases) than either serum icterus index or albumin-globulin ratio. The average age in the entire series was 54 years. There were only a few more men than women affected. Of the total number 61 were either heavy or moderate drinkers, 8 were teetotalers and the habits of the remaining 24 were unknown.

LEMUEL C. McGEE.

TRIER, E. Pain in infectious hepatitis. Acta Med. Scand., 128: Supp. 196: 392, 1947.

The symptoms of hepatitis are more varied than was previously realized. In the prevailing epidemics of jaundice in Denmark, many malignant cases of hepatitis are seen, especially in climacteric and elderly women. Abdominal pain occurs frequently and often resembles biliary colic. The pain may appear at any time in the course of the disease. The histories of illustrative cases are reviewed.

CHARLES A. FLOOD.

KUNKEL, H. G. AND HOAGLAND, C. L. Mechanism and significance of the thymol turbidity test for liver disease. J. Clin. Invest., 26: 1060 (Nov.) 1947.

A study was conducted on 200 patients with infectious hepatitis and 65 patients with other liver disease in the Out Patient Department of the Hospital of the Rockefeller Institute. Three ml. of the thymol reagent was added to 0.05 ml. of serum and turbidity measured by spectrophotometer. It is thought that the turbidity produced by the thymol reagent on lipemic sera from subjects without liver disease is due to an increase in the particle size of the protein-free lipid suspension, while that produced in clear hepatitis serum is due to the formation of a protein-lipid-thymol complex. The protein and lipid components appear to be intimately related in this reaction. The thymol turbidity test does not parallel the cephalin flocculation test either technically or clinically, although there is much similarity between the two. The cephalin flocculation test is likely to be positive earlier in liver disease than is the thymol turbidity test. This is probably due to the delay in rise of lipids in the disease. The tests, therefore, may both be profitably used during the course of the same illness, the cephalin flocculation being more sensitive early, and the thymol turbidity later.

SAM OVERSTREET.

ASHWORTH, C. T. Production of fatty infiltration of liver in rats by alcohol in spite of adequate diet. Proc. Soc. Exp. Biol. Med., 66: 382 (Nov.) 1947.

Recently, with the recognition of certain deficiency syndromes in the chronic alcoholic patient, there has been a tendency to attribute all of the organic changes in alcoholism to universal dietary deficiency.

Rats were given alcohol daily and either a high or low casein diet. Controls received similar diets and no alcohol. Food intake was regulated. Fatty infiltration of the liver occurred in every animal receiving alcohol and a low casein diet, alcohol and a high casein diet, and a low casein diet and no alcohol. No animals receiving the high casein diet and no alcohol had fatty infiltration of the liver. It is concluded that alcohol exerts an effect which permits accumulation of fat within the liver cells, and that this operates separately from that of extrinsic deficiency of lipotropic factors.

H. NECHELES.

### PANCREAS

COLP, R. The clinical significance of biliary, pancreatic and duodenal reflux. *J. Mt. Sinai Hosp., N. Y.*, 9: 257 (Sept-Oct.) 1947.

Dysfunctions of the sphincter of Oddi and the anatomical variations of the periampullary region of the duodenum are undoubtedly responsible for certain types of acute pancreatitis and cholecystitis, some forms of jaundice, and many of the unfavorable results following cholecystectomy. Although biliary reflux is not solely responsible for the pathogenesis of acute pancreatitis, the author cites a case in which bile entered the pancreatic ducts and caused a mild acute pancreatitis. Biopsies of pancreatic tissue are seldom taken because of the fear of causing acute pancreatic inflammation. If this procedure were done more regularly it is probable that it would be found that bile is responsible for the many cases of pancreatic edema and acute pancreatitis. Pancreatic reflux is probably more frequent than biliary reflux. In a case recently observed, periodic spasm of the sphincter was definitely shown by lipiodol studies and recorded by kymographic tracings, and its role in the causation of a pancreatic reflux was further evidenced by the occasional presence of amylase in the biliary drainage. The re-

flux of duodenal contents through the common bile duct is exceedingly rare.

ALBERT CORNELL.

LAGERLÖF, H. O. Normal serum esterase and pancreatic lipase in diseases of the biliary ducts and pancreas. *Acta Med. Scand.*, 128: Supp. 196: 399, 1947.

The pancreatic serum lipase may be elevated in acute attacks of biliary and pancreatic disease, pancreatic carcinoma, spasm of the sphincter of Oddi, peritonitis following perforation with escape of duodenal juice into the peritoneal cavity, and probably also in ileus. The elevation of serum lipase resembles that of serum amylase, but the two enzymes are not wholly parallel. Elevated serum lipase is usually a sign of damage to the pancreatic parenchyma or stasis in the pancreatic ducts. The normal serum esterase is not significantly influenced by the elevation of the pancreatic lipase occurring in biliary and pancreatic diseases. The method chosen for routine diagnostic study of pancreatic disease is the serum amylase. When high normal values for amylase are obtained, the lipase may be found to be elevated.

CHARLES A. FLOOD.

MORLEY, J. Carcinoma of the ampulla of Vater. *Brit. J. Surg.*, 34: 146 (Oct.) 1947.

Seven cases of carcinoma of the ampulla of Vater are reported. One presented an apparent spontaneous cure. The other 6 cases were treated by a two-stage operation—the first stage consisting of a cholecystostomy and gastrojejunostomy, and the second stage including resection of the second part of the duodenum and a considerable portion of the head of the pancreas, with ligature but no anastomosis of the pancreatic duct. The two-stage procedure is preferred as it is believed to be less hazardous to the patient. Cholecystostomy is advocated as less likely to be followed by cholangitis than is an anastomosis between the common duct and the jejunum. A stoma 1.5 cm. in length seems adequate to prevent stenosis. Since patients with ligation of the pancreatic duct compensate most satisfactorily for the absence of pancreatic trypsin, lipase and amylase, this procedure seems to be a safer one than does an anasto-

mosis of the pancreatic duct to the jejunum with resultant possibility of fistula formation.

J. DUFFY HANCOCK.

BEGTRUP, H. AND TAGE-HANSEN, E. Studies on plasma-prothrombin following pancreatectomy. *Acta Physiol. Scand.*, 14: 189 (Nov.) 1947.

In order to determine whether the pancreas is necessary for the formation of prothrombin, it was decided to remove the pancreas experimentally on 6 dogs and then follow the prothrombin level in the blood. The fall in the prothrombin levels was moderate and lasted at least a week before definitely subnormal values were seen. In cases of experimental partial or total removal of the liver the fall of prothrombin, which was very pronounced, occurred in 6 to 24 hours. It therefore appears that prothrombin formation must still take place after pancreatectomy. The pancreas is not essential then to the formation of prothrombin. It is probable that both pancreatectomy and certain diseases of the pancreas in which the function of the gland ceases may affect the liver in such a way as to reduce its prothrombin-forming capacity.

ALBERT CORNELL.

STRÖMBECK, J. P. Increased amylase concentration in urine as a sign of choledocholithiasis and acute pancreatic disease. *Acta Med. Scand.*, 128: Supp. 196: 411, 1947.

The author studied 72 patients with cholelithiasis who exhibited a rise in urinary amylase concentration and came to operation. It is believed that an increase in urinary amylase excretion signifies pancreatic damage. In this series of cases, between one-half and two-thirds of the cases were found to have no gross evidence of pancreatitis at operation. The remaining patients exhibited circumscribed infiltration of the pancreas with or without fat necrosis. Operation was carried out in all cases within 30 days. It is believed that the rise in urinary amylase is due either to ductal spasm or stone in the papilla. A "common channel" mechanism for production of pancreatitis does not seem to have been established

and stasis in the pancreas alone may be sufficient. The presence of a separate opening for the duct of Santorini, found in about 20 per cent of the cases, may play a role in the prevention of pancreatic stasis.

CHARLES A. FLOOD.

### ANEMIAS

HANSEN-PRUSS, O. C. Relapse of patients with pernicious anemia receiving folic acid. *Am. J. Med. Sci.*, 214: 465 (Nov.) 1947.

This is a report on two patients with pernicious anemias, who relapsed while receiving folic acid. A 43-year old man, seen in relapse after discontinuing liver therapy, responded well to 30 mg. of folic acid daily and maintained the level of his erythrocyte count and hemoglobin for 5 months on 5-10 mg. of folic acid daily. He then relapsed while on this medication and did not respond to increased doses of folic acid. Liver extract was promptly effective. The other patient was a 63-year old male with untreated pernicious anemia when first seen. His erythrocyte count was 1,210,000. When given 30 mg. of folic acid daily his reticulocyte count rose to 29 per cent on the 9th day. After 90 days treatment on a maintenance dose of 5-10 mg. daily, he had 3,600,000 erythrocytes with persisting macrocytosis. This was followed by hematologic relapse which persisted even though the daily dose of folic acid was raised to 30 mg. Liver extract parenterally promptly brought about improvement. The author concludes that "folic acid, administered by mouth, therefore, seems to lack some of the properties of purified liver extract administered parenterally."

LEMUEL C. McGEE.

AGREN, G. AND WALDENSTROM, J. The intrinsic factor activity of highly purified preparations of aminopolypeptidase II. *Acta Med. Scand.*, 128: Supp. 196: 432, 1947.

In a previous report, the authors have shown that small doses of liver digested with aminopolypeptidase had anti-anemic activity in cases of pernicious anemia. The present study demonstrates an anti-anemic activity

obtained by incubating beef muscle with a purified aminopolypeptidase solution prepared from the pyloric portion of hog's stomach. Extract of pyloric end of hog's stomach alone was found to be inactive in one case but may have been active in another. Extract of pyloric portion of hog's stomach incubated with beef muscle which had been predigested with pepsin, produced a factor which caused a remission in cases of pernicious anemia. The remissions in pernicious anemia after treatment were indicated in several ways. It was found that the megaloblastic bone marrow reverted to a normoblastic marrow. A marked drop in serum iron values, usually to subnormal, occurred. Reticulocyte responses took place after treatment, followed by an increase in the platelet count. Increase in the red count and hemoglobin were demonstrated in only one or two of the studied cases because of shortage of the active substance.

CHARLES A. FLOOD.

### ULCER

MOORE, F. D. Current practices in the surgical treatment of ulcer. *Surg. Clinics N. Am.*, 1071 (Oct.) 1947.

In the light of two new developments in the surgical treatment of peptic ulcer, (i.e., reduction in the mortality of subtotal gastrectomy to about 2 per cent and introduction of vagotomy) it is now possible to define more accurately the status of surgical therapy. Acute perforations are treated surgically within the first 12 hours and treatment is limited to simple closure of the ulcer with painstaking aspiration of the peritoneal cavity, and the use of penicillin or streptomycin depending on the character of cultures. In the case of acute massive hemorrhage, subtotal gastrectomy is advised primarily in the older age group (over 55 years) with adequate replacement of blood. The treatment for true obstruction is subtotal gastrectomy. In the case of gastric ulcers which stand as a "threat of malignancy", the therapy for all lesions proximal to the pylorus should be basically surgical.

Vagus resection will find use primarily in the treatment of the intractable, unobstructed, not acutely bleeding duodenal or

jejunal ulcer. The recurrence rate following vagus resection does not differ significantly from that following subtotal gastrectomy. Further time is required before complete evaluation of vagotomy can be made.

FRANK G. VAL DEZ.

LITTLE, J. M., OGLE, B. C., YEAGLEY, J. D., AND CAYER, D. Effect of tetraethylammonium chloride in experimental gastric ulceration in the rat. *Science*, 105: 448 (Nov.) 1947.

The effectiveness of tetraethylammonium chloride (Etamon Chloride) in prevention of the development of gastric ulceration in rats was tested on a group of eighteen female rats—nine of whom were used as controls. The pylorus was ligated through an abdominal incision after the rats had been fasted for 72 hours. Nine of the rats received no treatment while nine were given hourly injections of Etamon Chloride in saline. Two of the control rats died shortly after operation but of the 7 surviving all died in less than 8 hours and at autopsy showed ulceration in the stomach with perforation. Several showed multiple ulcers. Of the nine receiving the Etamon Chloride five showed single ulcers; there were no multiple ulcers and only once had perforation occurred. The shortest survival time was 7.1 hours in the four rats who died. The remaining five were sacrificed at 9.7 hours or longer postoperatively.

"Altho Etamon Chloride did not completely prevent gastric ulceration in this series, on the basis of survival time, perforation, and incidence of ulceration, it appears that it was definitely beneficial."

SAM OVERSTREET.

DRAGSTEDT, L. R., HARPER, P. V. JR., TOVEE, E. B., AND WOODWARD, E. R. Section of the vagus nerves to the stomach in the treatment of peptic ulcer. Complications and end results after four years. *Ann. Surg.*, 126: 687 (Nov.) 1947.

Dragstedt and his associates have resected the vagus nerves in 212 patients with various types of peptic ulcer. One patient died of aspiration pneumonia—an operative mortality of less than 0.5%. Other undesirable

sequelae have been intercostal pain, pleural effusion, pulmonary atelectasis, delayed emptying of the stomach, and diarrhea. Few sequelae have been serious. Dragstedt now prefers the transabdominal approach so as to be able to deal with cicatrical obstruction, when it exists. Posterior gastroenterostomy is performed in about one-third of the patients for whom a transabdominal vagal section is done for duodenal ulcer. Nineteen patients, out of a group of 35 with duodenal ulcer and in whom vagus section alone was done, displayed transitory symptoms of gastric retention. Two later required a gastroenterostomy.

To reduce the problems resulting from decreased gastric tonus and motility, use of a Levin tube and the Wangensteen suction apparatus for five days following vagus section is urged. Vagus section is physiologically possible because of the well-known local automatism inherent in the stomach wall. The sudden removal of the tonic effect of the vagus nerves leaves the inhibitory influence of the sympathetic extrinsic nerve supply unopposed. Maintaining gastric decompression during the transition state (i.e. until the local automaticity of the stomach is adequate) is "perhaps the most important single item in postoperative care."

There is a reduction of over 60 per cent in the total hydrochloric acid output from the stomach after complete vagus section. If one small vagus fiber to the stomach remains intact the ulcer symptoms persist or recur and gastric secretion is not diminished. In patients who had complete vagus sections three and four years ago there has been no return to normal of the total hydrochloric acid output of the stomach nor a return of the response to insulin.

LEMUEL C. McGEE.

#### MOORE, F. D. Vagus resection for ulcer:

An interim evaluation. II. Clinical results. *Ann. Surg.*, 126: 664 (Nov.) 1947. Moore reviewed the clinical results 2 to 30 months after the operation in 74 patients undergoing vagus resection for peptic ulcer. Eighty-seven per cent had satisfactory results. The most common gastrointestinal side effect of the operation was diarrhea,

usually of a minor or transient degree. This symptom was reported in more than half the patients. Transient upper abdominal fullness also was common. No criteria is suggested for the detection of patients who may be likely to have a bad result from vagus resection.

LEMUEL C. McGEE.

#### RANSOM, H. K. Subtotal gastrectomy for gastric ulcer: A study of end results. *Ann. Surg.*, 126: 633 (Nov.) 1947.

Between 1925 and 1945, 1,356 patients with gastric ulcer were treated in the Hospital of the University of Michigan. Two hundred forty-six (18.9%) received surgery. Of this number 188 patients had some form of gastrectomy. There were 15 operative deaths, a mortality of 7.9 per cent. Ten per cent of the group were found on histologic study to have malignant disease "superimposed on an old chronic ulcer." The five-year survival rate of those with cancer was 40 per cent. A follow-up 2-20 years later was possible on 108 living patients and 47 who died, in the group receiving surgery. Deaths were due chiefly to cardiovascular disease (18), pulmonary disease (9), and trauma (8). Of the living patients, 92 per cent have satisfactory results. Only four verified jejunal ulcers were found postoperatively.

LEMUEL C. McGEE.

#### WALTERS, W., NEIBLING, H. A., BRADLEY, W. F., SMALL, J. T., AND WILSON, J. W. A study of the results, both favorable and unfavorable, of section of the vagus nerves in the treatment of peptic ulcer. *Ann. Surg.*, 126: 679 (Nov.) 1947.

The authors prefer the transabdominal approach for section of the vagus nerves. In 23 of 40 patients reviewed here, gastric operations in addition to neurectomy were performed. The results were variable. Measurable reduction in acidity occurred in most patients. Relief of pain is attributed to release of "gastropasm," reduction of acidity through the interruption of cephalic stimulation, and possibly other factors not yet recognized. At least one ulcer has been known to recur. The status

of the operation in the minds of the authors is still in the investigative stage.

LEMUEL C. McGEE.

## SURGERY

HUME, J. B. AND BLACKBURN, G. Synchronous combined total gastrectomy. *Brit. Med. J.*, 4533: 817 (Nov.) 1947.

The authors state that the present position of surgery in relation to carcinoma of the stomach is unsatisfactory, and that the immediate mortality from total gastrectomy for malignant disease is too high. Combined excision through a thoracic and an abdominal wound by two surgeons working synchronously is suggested as a means of reducing the time of operation and the morbidity and mortality. The time of operation should be 2 to 2½ hours in an uncomplicated case—the abdominal surgeon doing the division of the duodenum, lower stomach mobilization and Roux anastomosis, and the thoracic operator the mobilization of esophagus and cardia and the esophago-jejunostomy.

JOSEPH B. KIRSNER.

BARTLETT, M. K. The status of pancreaticoduodenal resection. *Surg. Clinics N. Am.*, 1032 (Oct.) 1947.

Of 78 patients with a diagnosis of carcinoma of the pancreas, the ampulla of Vater, or the duodenum at the Massachusetts General Hospital, 65 (83%) were subjected to surgery. Twenty-five of these cases had radical pancreaticoduodenal resection. Eleven were one-stage procedures with an operative mortality of 45 per cent; 14 patients had two-stage resections with an operative mortality of 29 per cent. Of these, 2 are still living, one 8 months and one 5 years after operation. The average survival period in both one- and two-stage procedures was 7 months. The average survival in patients who had palliative operative procedures was 5 months.

It is evident from the above that the present treatment is far from satisfactory, however, the only logical attack at the present time is radical resection. The location of the primary tumor and the presence or absence of lymph node metas-

tases had no demonstrable effect on the survival period in this series.

FRANK G. VAL DEZ.

BARNES, C. G. Hypoglycemia following partial gastrectomy. *Lancet*, 253: 536 (Oct.) 1947.

Three patients with subtotal gastrectomy were investigated because of symptoms of hypoglycemia coming on about 1 to 2 hours after meals. X-ray examination revealed that the gastric emptying time in each case was not longer than 15 minutes. Sugar tolerance tests confirmed the hypoglycemic blood levels which corresponded to the onset of symptoms. The type of curve has been described as the oxyhypoglycemic or lag curve, and is explained on the basis of rapid absorption of sugar because of the rapid emptying of the stomach. Preceding this initial fall in blood sugar level, there is a rapid rise to hyperglycemic levels with glycosuria. The rapid fall is due, in the author's opinion, to an increased insulin sensitivity. He feels that this does not develop until some time after operation and is the response to the persistent hyperglycemia. Treatment consisted of high fat, low carbohydrate diet in 1 case, which reduced insulin sensitivity and gave relief of symptoms. In the other 2 cases, who would not accept the diet, treatment was symptomatic. In these 2 patients, the attacks ceased spontaneously after a while.

PHILIP LEVITSKY.

KLINGENSTEIN, P. Surgical management of gastrojejunocolic fistula. *J. Mt. Sinai Hosp., N. Y.*, 9: 449 (Sept.-Oct.) 1947.

Gastrojejunocolic fistula is a life-threatening complication of gastroenterostomy. As opposed to gastrojejunal ulcer, which may respond to medical therapy, surgical management in the former is imperative. Technically, the procedure is difficult and time-consuming. Ideally, operation should aim to excise the fistula and reconstruct the parts along with gastrectomy, but each case must be evaluated individually. In some, the general condition of the patient will contraindicate so lengthy a procedure. In others, the local condition because of its size and infectious potentiality will warrant a

staged procedure. The author reviews 8 operated cases of gastrojejunocolic fistula. In some, operation was completed in one stage. Ascending colostomy was done in others as a preliminary procedure. There was 1 death. The operative mortality, which was formerly extremely high, can be kept low by adequate preoperative preparation and the selection of a staged procedure. Gastrectomy should be part of the operative procedure whenever feasible.

ALBERT CORNELL.

#### PHYSIOLOGY: SECRETION

HORSTMANN, P. Contributions to the understanding of the regulation of the gastric acidity. *Acta Physiol. Scand.*, **14**: 27 (Nov.) 1947.

The present investigation is based upon examination of gastric juice obtained from 87 human individuals, with and without peptic ulcer and gastritis, by means of intravenous injection of 20 units of insulin. The acidity, chloride, pepsin, and rate of secretion were determined also without the use of a stimulating agent. Acidity and chloride show a strong parallelism, in common fasting juice as well as in secretion following insulin stimulation. The graphic expression of the relation between acidity and chloride is very nearly rectilinear. Calculations based on the secretory hypothesis of Pavlov show that a rectilinear interdependence of acidity and chloride must be expected, when considering the actual acidity of the gastric juice as resulting from a mixture of an acid secretion of constant acidity with a non-acid secretion. The acid component, which is supposed to be a solution of pure hydrochloric acid is computed to have an acidity and a chloride concentration of approximately 180 m.eq./L., whereas the chloride of the non-acid component is approximately 70-80 m.eq./L. The non-acid secretion probably possesses an alkalinity of approximately 35 m.eq./L. It is not likely that the chloride concentration of the non-acid component is dependent on the acidity. The chlorides of the non-acid diluting fluid probably originate from various sources. An account is also given of current theories concerning secretion of gastric juice and of the way in

which the stomach regulates the acidity of its contents.

ALBERT CORNELL.

PERRY, E. L. AND HORTON, B. T. Use of pyribenzamine in prevention of histamine-induced gastric acidity and headache and in treatment of hypersensitivity to cold. *Am. J. Med. Sci.*, **214**: 553 (Nov.) 1947.

In 14 human subjects pyribenzamine (50 mg. twice daily up to 100 mg. four times daily) usually failed to prevent the increase in gastric acidity induced by histamine.

Three of 4 human subjects had less intense and shorter histamine headache after administration of pyribenzamine than before. Each of 3 subjects hypersensitive to cold were given symptomatic relief by pyribenzamine intravenously. Urticaria and edema disappeared shortly after the drug was given in two of the latter patients.

LEMUEL C. McGEE.

IHRE, B. J. E. Studies in gastric secretion with an improved histamine test. *Acta Med. Scand.*, **128**: Supp 196: 322, 1947.

The author reports the results of a series of histamine tests carried out with continuous suction and a single lumen tube. The mean volume of secretion in duodenal ulcer cases was higher in males than in females. In gastric ulcer the volume was also higher in men than in women although the difference in this instance was not statistically significant. A secretory volume of more than 180 ml. per hour was regarded as hypersecretion, this being two times the standard deviation from the mean. In a comparison between the histamine test and gastroscopic findings, it was observed that acidity values under 90-100 m.eq. at a secretion volume of at least 50 ml. per hour indicates the existence of chronic gastritis. Higher acidity values did not rule out the existence of chronic gastritis. Acidity values which reached 130-140 m.eq. were indicative of a normal mucosa on endoscopic examination.

Comparison of the existence of an "increased secretion layer" shown roentgenologically and a hypersecretion found in the histamine test showed that an "increased secretion layer" is not a reliable sign of

hypersecretion and that it is found with the same frequency in hypersecretion as in cases with normal secretion. Other factors such as regurgitation of duodenal contents into the stomach may account for the X-ray finding of an "increased secretion layer."

CHARLES A. FLOOD.

PALMER, E. D. The effect of short-wave diathermy on the secretory activity of the fasting normal human stomach. *Am. J. Dig. Dis.*, 14: 342 (Nov.) 1947.

The author presents a brief review of previous studies of the effect of diathermy on the secretory activity of the animal and also the human stomach. His own studies were carried out on 10 volunteers in whom the gastric secretory activity was determined before, during, and after diathermy administration over the gastric region. As a result of this study it is concluded that short wave therapy has no demonstrable effect on the total secretion or total acid production of the normal fasting human stomach.

HENRY TUMEN.

#### MISCELLANEOUS

RAY, B. S. AND NEILL, C. L. Abdominal visceral sensation in man. *Ann. Surg.*, 126: 709 (Nov.) 1947.

The authors have studied visceral sensation in patients before and after sympathectomy in which the splanchnics and ganglionated chain were removed from the seventh thoracic through the third lumbar ganglia on one or both sides. Pain sensation in the stomach and intestines (except the rectum), extra hepatic biliary tract, pancreas, kidney, and ureter is mediated wholly by visceral afferent nerves accompanying sympathetic nerves. The kidney, ureters and two sides of the colon have a homolateral sensory supply. The remaining abdominal organs, with the possible exception of the gastric mesentery, have a bilateral sensory supply.

Pressure, equivalent to 2 cm. of mercury, in the small intestine caused a deep aching pain. If the balloon was in the jejunum or upper ileum the pain was located at or above the umbilicus, if in the terminal ileum the pain was below the umbilicus and occasionally about McBurney's point. Pain

reception appears to exist not in the walls of the stomach and intestine but in the mesenteric-visceral juncture. There is a sensation of heat if the temperature inside the stomach is raised to 110° or 120° F., and a sensation of cold if lowered to 32°. The sensation is located in the sub-xiphoid region.

The loss of visceral pain sense alters a patient's response to visceral disease. For example, two patients who had had bilateral thoracolumbar sympathectomy sustained perforated peptic ulcers without feeling pain. Vomiting and signs of acute peritonitis led to diagnosis and successful operation.

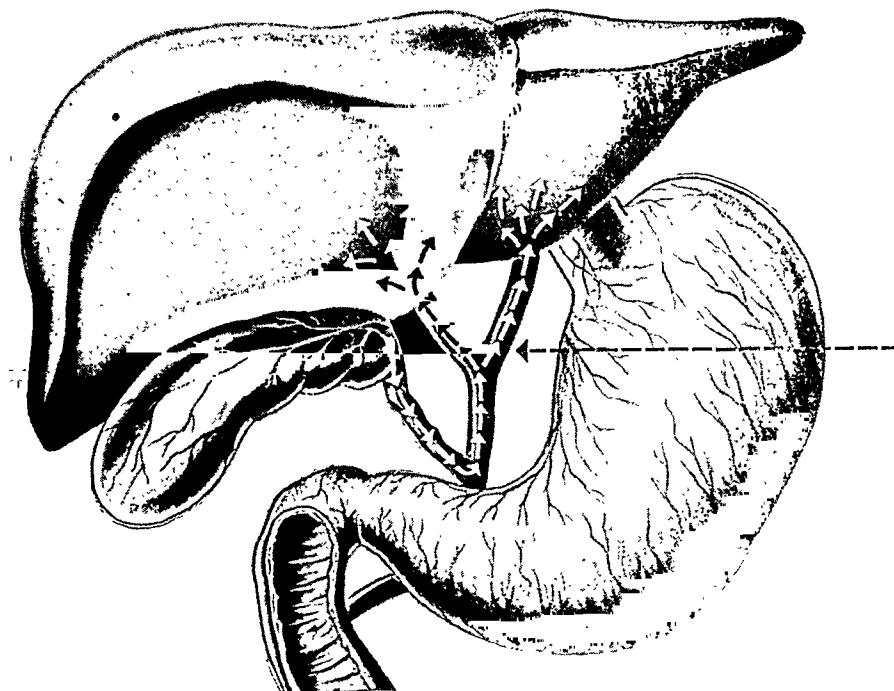
LEMUEL C. McGEE.

NOBACK, C. R. AND MONTAGNA, W. Histochemical studies of the basophilia, lipase and phosphatases in the mammalian pancreas and salivary glands. *Am. J. Anat.*, 81: 343 (Nov.) 1947.

This paper presents the results of histochemical studies of the pancreas of the mouse, rat and man, and of the salivary glands of the mouse and rat. The studies were made to ascertain the nature of the basophilia and the presence of lipase, alkaline and acid phosphatase. The basophilia described appear to represent ribonucleoproteins. In the pancreas, during phases of maximal protein synthesis there is an increased intensity of the chromidial basophilia. The lipase reaction is intense in the distal portions of the resting acinar cells of the pancreas. After pilocarpine stimulation, this lipase activity is reduced. Alkaline and acid phosphatase are present in the parenchymal cells of the pancreas. Alkaline phosphatase is moderate to weak in some of the peripheral islet cells. Acid phosphatase is intense especially throughout the islets of Langerhans. All of the salivary glands contain some degree of alkaline and acid phosphatase activity. The alkaline phosphatase reaction is especially intense in the serozymogenic cells of the submaxillary gland. Although all the salivary glands may secrete salivary phosphatase, it appears that in the mouse and rat, most of the salivary phosphatase is secreted by the serozymogenic cells of the submaxillary gland.

ALBERT CORNELL.





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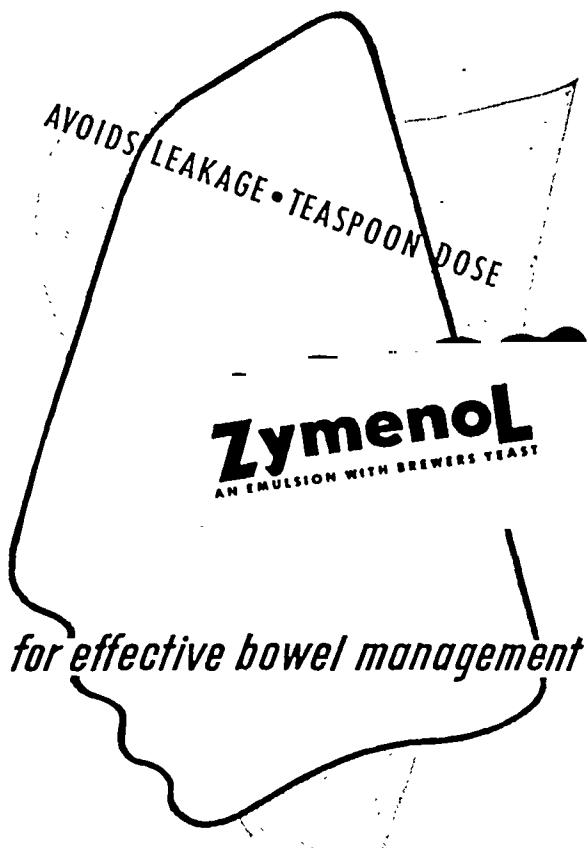
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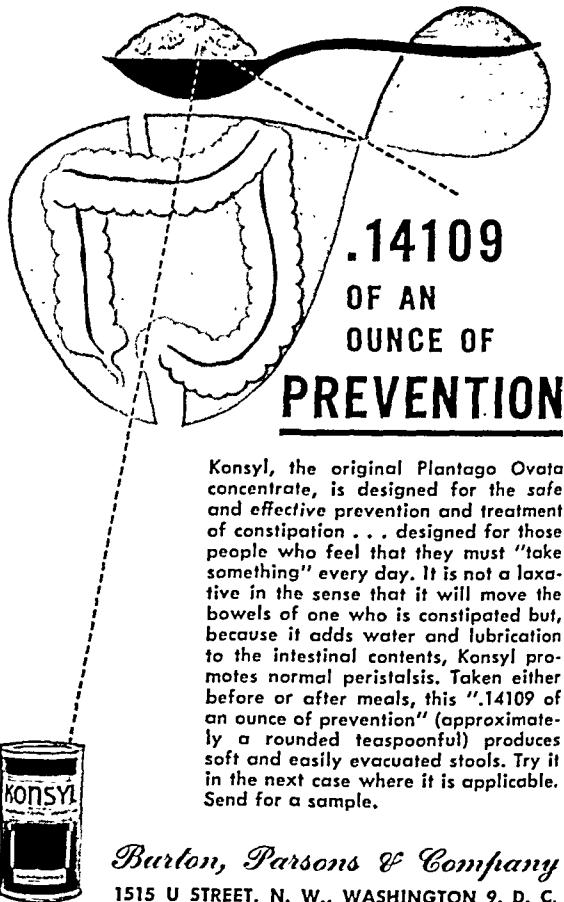
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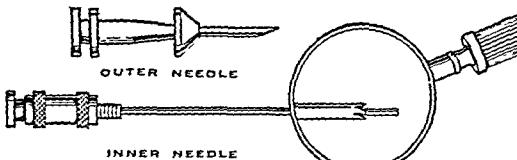
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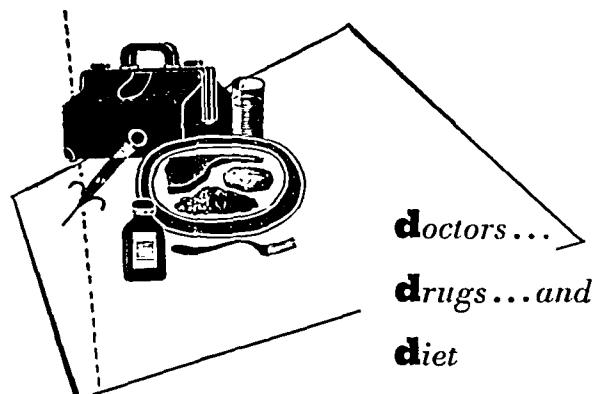
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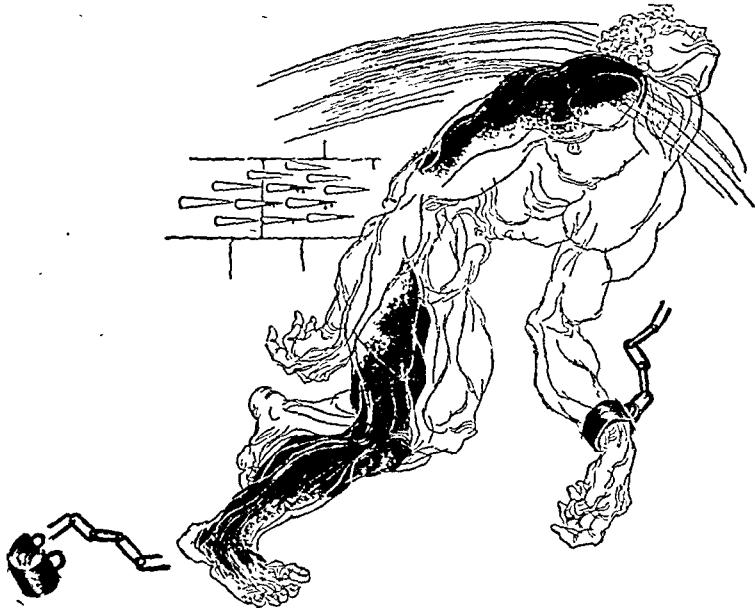
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ASSOCIATION .....

779

VOLUME 11, NUMBER 5

## GASTROENTEROLOGY

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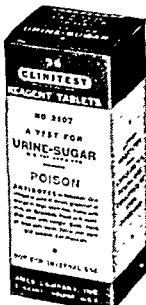
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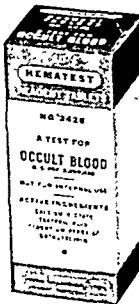
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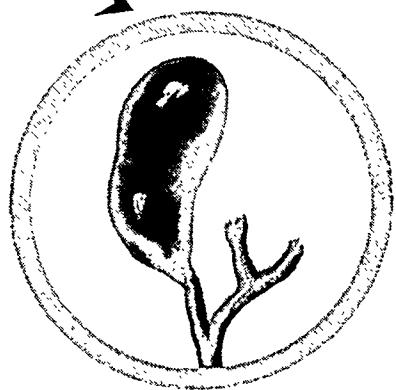
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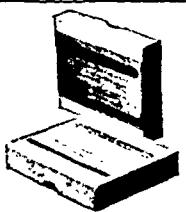
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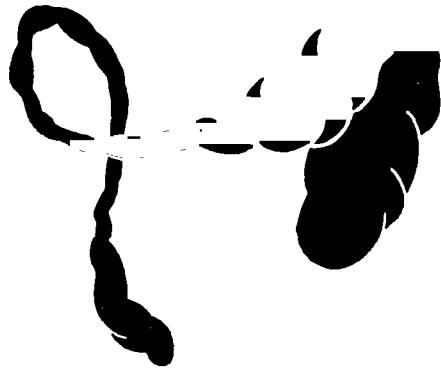
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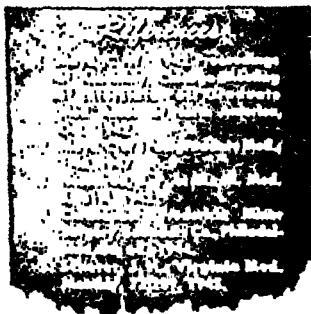
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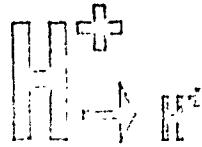
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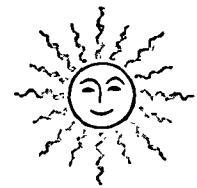
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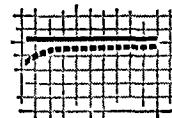
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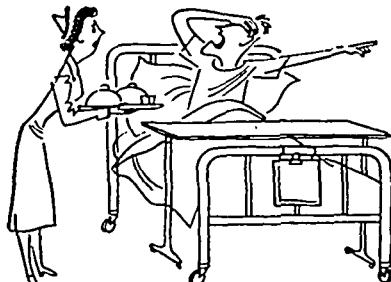
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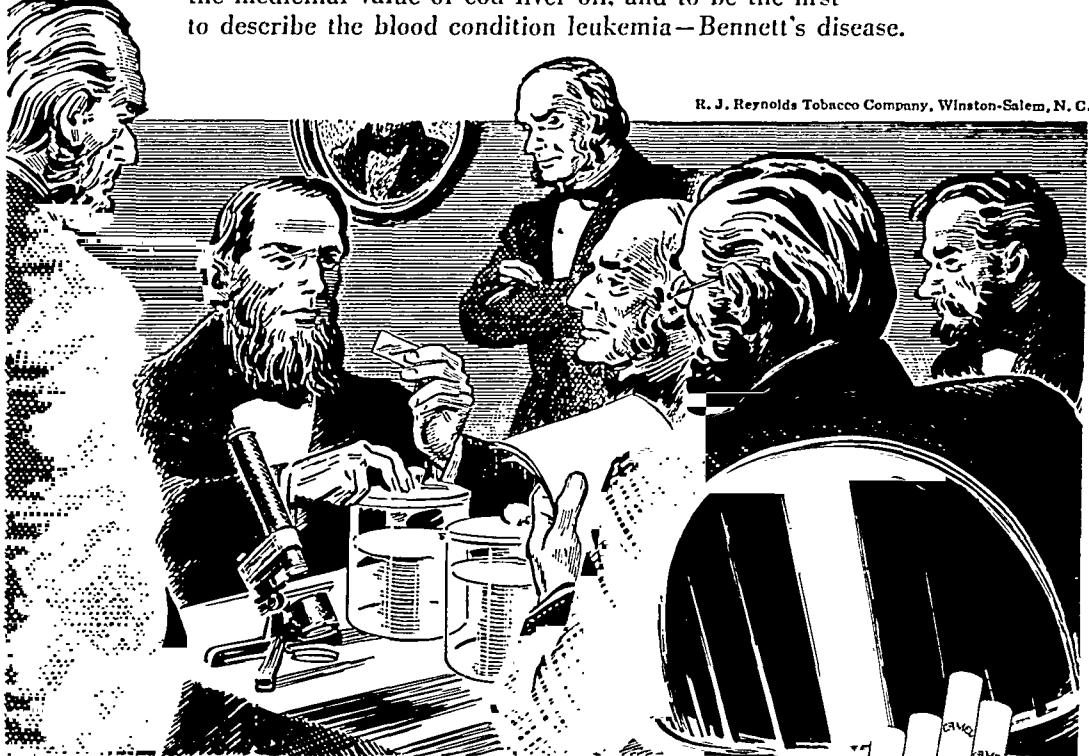


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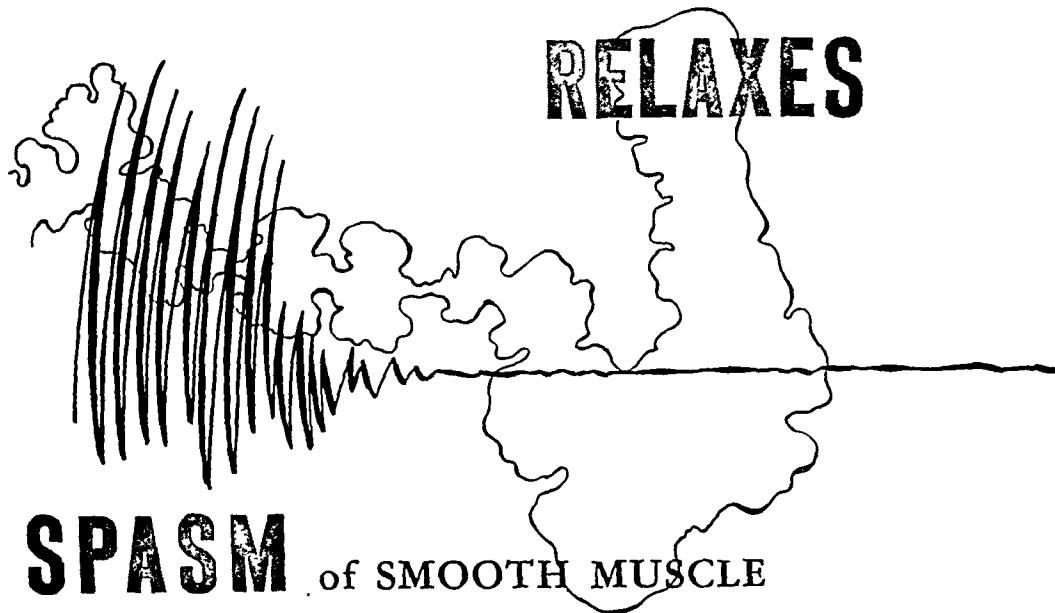


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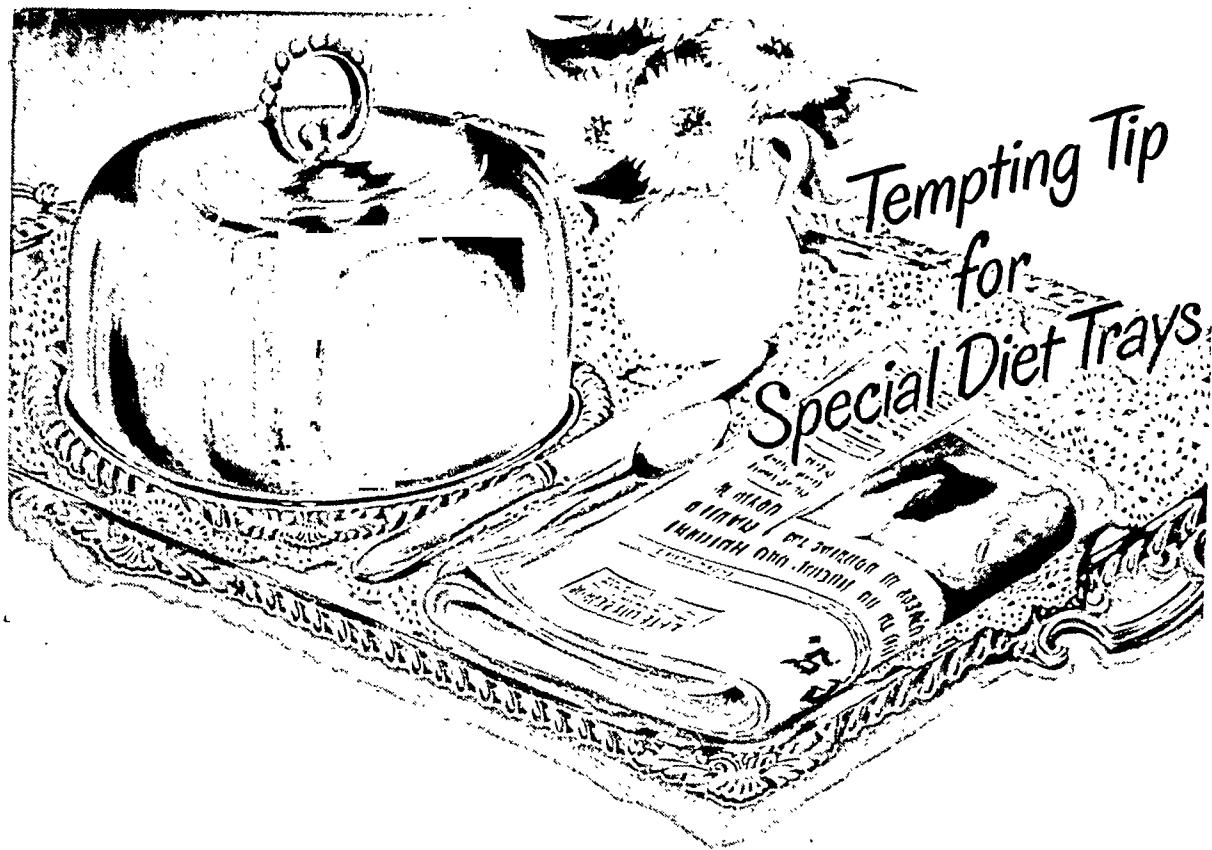
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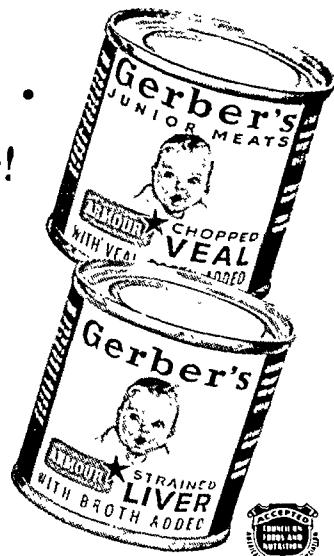
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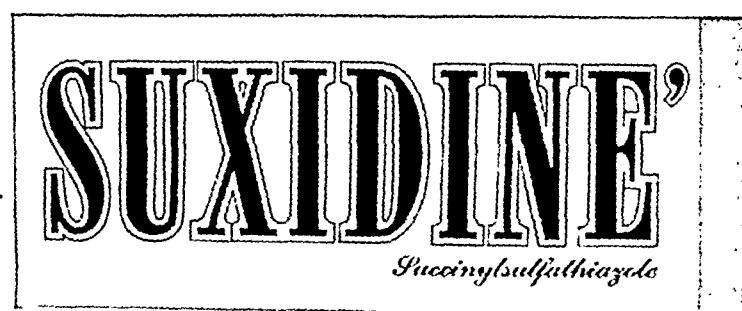
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# GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*

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November 1948

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## GASTRIC ULCER: A STUDY OF 600 CASES

FRANCES H. SMITH, M.D., AND SARA M. JORDAN, M.D.

*Department of Gastroenterology, The Lahey Clinic, Boston, Massachusetts*

### INTRODUCTION

An estimated incidence of 80,000 cases of gastric cancer in this country, with a death rate of 40,000 per year, is indeed an effective spur to the adoption of any prophylactic or therapeutic measure by which this afflictive evil can be combated. That a certain percentage of these cases have their origin, as a wolf in sheep's clothing, in the form of gastric ulcer, there is now no doubt. In the estimation of our pathologist they constitute 20 per cent or less of the total group of cancer of the stomach. In contrast to the other three groups of manifestly malignant lesions—the polypoid lesion which protrudes into the lumen, the obviously ulcerating carcinoma, usually with only one side definitely bordered, or the diffusely infiltrating lesion—this group of cases which look like ulcer can reasonably be thought to be benign. Yet, either from their beginnings on they are not benign, or they change from a once benign character to a later malignant one.

Differentiation between benign and malignant gastric ulcer, with all the diagnostic and therapeutic problems involved in this issue, should excite investigation, contemplation and reasoned judgment, and first of all, investigation, because it alone is the logical precursor of meditation and reasoned judgment. In the spirit of investigation of this problem, therefore, this study of 600 cases of gastric ulcer was undertaken.

In an earnest search for the greatest therapeutic good for the greatest number of patients, one is confronted with the question: Is the situation so perilous that all patients with gastric ulcers shall be submitted to gastric resection and the differentiation between benign and malignant lesions be left to the pathologist? Or, on the other hand, shall gastroenterologists continue their attempts to distinguish between those gastric ulcers which can be trusted to be benign, and those which are or may become malignant? This issue is of tremendous importance even in these days when, with the advance of skill in surgery and anesthesia, the risk of resection has markedly decreased. An established and generally accepted policy of resection of all gastric ulcers means that throughout the country, wherever surgery is done, benign ulcers, if on the

proximal side of the pylorus, will be resected. As a result of this policy, a certain number of individuals with benign ulcers which would have healed under medical treatment will have died as a result of the operation, and a relatively large number of persons will be living with the physiologic abnormality of having only one-third or less of their stomachs.

Considered judgment and not snap decision is required. In this regard it may not be amiss to call attention to the very human frailty, of which most of us are guilty, of being swayed in our judgment by our last or most striking

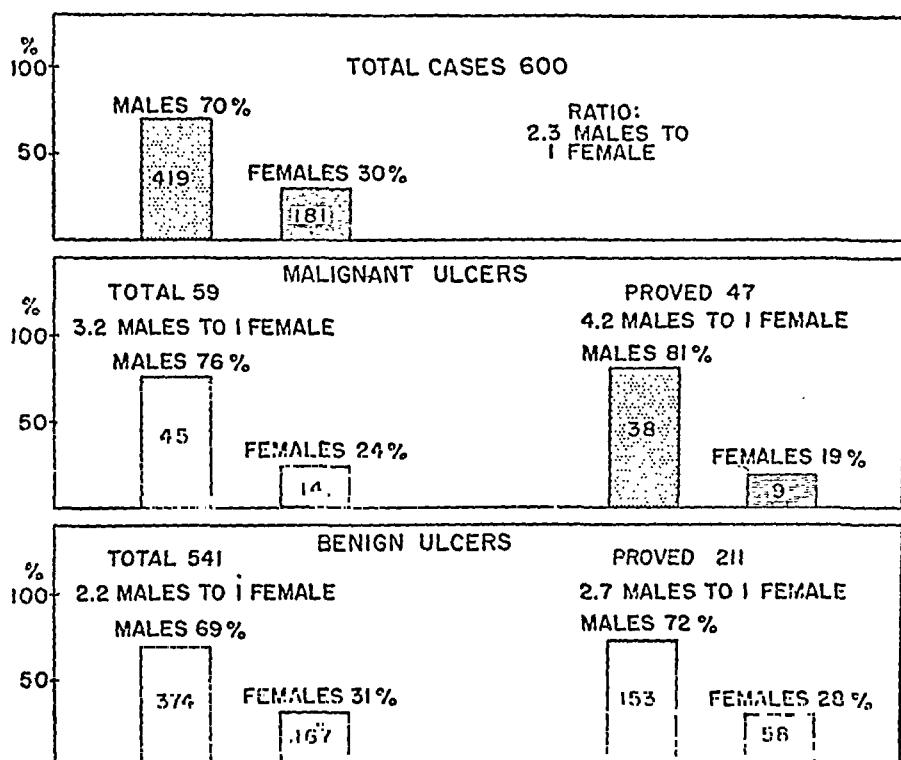


FIG. 1. 600 CASES OF GASTRIC ULCER—SEX INCIDENCE

experience. An ulcer treated too long as benign and later found to be inoperable or in a late stage of malignancy makes a poignant and unforgettable impression upon all concerned; but no less keen is the impact upon memory and medical conscience of the patient with ulcer histologically proved benign, who has died right after resection of the stomach. We must also be prepared to confront the physiologic and functional disorders which may to some degree, at least, follow resection—justified most certainly if malignancy, actual or potential, or intractability has existed, but equally certainly regrettable if this is not the case.

Before suggesting a possible solution to the problem outlined, we wish to

present the statistical data obtained in this study of 600 cases. This material is presented in four categories: first, the malignant ulcers; second, the benign operated ulcers; third, the benign nonoperated ulcers and fourth, a comparison of the findings in the benign and malignant groups.

Figure 1 gives the sex incidence for the entire group, the total benign and the total malignant group as well as that in the proved benign and proved malignant cases. Here it is of interest to note that whereas the total group and the proved benign group show a preponderance of males in the ratio of approximately 2 males to 1 female, the proved malignant group shows the ratio to be 4 males to 1 female, or almost twice as much.

#### MALIGNANT ULCERS—59 CASES

The incidence of malignant gastric ulcers in the entire group was 9.8 per cent. Table 1 shows that 47 of these 59 cases were histologically proved and that 12, although clinically considered to be malignant, were not operated on for the reasons stated.

TABLE 1  
*600 Cases of Gastric Ulcer*  
*Analysis of 59 Malignant Ulcers*

- 
- |    |  |
|----|--|
| 44 | operated on and proved pathologically  |
| 12 | not operated on because of refusal, age or concomitant disease but clinically presumed to be malignant |
| 2  | treated as benign but proved at postmortem examination (6 and 23 years later) to be malignant          |
| 1  | diagnosed as malignant, refused operation, and proved by postmortem examination to be malignant        |
- 

Table 2 shows the number and type of operations performed. It is important to note that in only 75 per cent of the patients with malignant gastric ulcers was the lesion resectable at the time of operation.

Table 3 lists original diagnoses after the initial clinical and roentgenologic survey had been completed.

Table 4 gives the length of follow-up preceding operation. Fifty-four and five-tenths per cent of the patients with malignant gastric ulcers were operated on within two months from the time they were first seen at the Lahey Clinic. The others were operated on at intervals varying from two months to seven years. Of the 5 patients who were not operated upon until two to four months after they were first seen, two patients refused immediate hospitalization. Two were the victims of delayed hospitalization and one was operated on because of persistence of symptoms although no lesion had been demonstrated by roentgenogram before operation.

Of the 5 patients whose operations were delayed four to six months, 1 patient did not return for roentgenograms for four months; 2 were operated upon be-

TABLE 2  
*600 Cases of Gastric Ulcer*  
*Analysis of 44 Operated Malignant Ulcers*

TYPE OF OPERATION	NUMBER OF CASES
Total gastrectomy*	2
Partial gastrectomy*	31
Laparotomy	8
Gastrostomy	1
Anterior jejunostomy	1
Suture of perforation	1

\* Resectability rate, 75 per cent.

TABLE 3  
*600 Cases of Gastric Ulcer*  
*Analysis of 44 Operated Malignant Ulcers*

ORIGINAL DIAGNOSIS	CASES	
	Number	Per cent
Malignant.....	21	47.8
Benign*	23	52.2

\* 50 per cent of these patients later operated on because of recurrence.

TABLE 4  
*600 Cases of Gastric Ulcer*  
*Analysis of 44 Operated Malignant Ulcers*  
*Length of Follow-up Preceding Operation*

DURATION	NUMBER OF CASES
1 month or less	17
1 to 2 months	7
2 to 4 months	5
4 to 6 months	5
6 to 12 months	1
1 to 2 years	2
2 to 5 years	5
5 to 7 years	2

cause of persistence of symptoms and 2, although all clinical and roentgenologic signs of ulcer disappeared after treatment, because of recurrence.

The 10 patients operated upon later than six months had had medical management in or out of the hospital and were operated upon because of recurrence.

Table 5 gives the mortality statistics in the 44 cases of operated malignant ulcers. None of these deaths occurred after resection; 4 followed laparotomy and 1 the suture of a perforation.

Table 6 gives the survival period in the 33 patients with malignant ulcer who had gastric resection. Only 5 of this group, or 15.1 per cent, were alive after five years. One of these patient who was found to have a lymphosarcoma at operation was alive and well nine years later.

TABLE 5  
600 Cases of *Gastric Ulcer*  
Analysis of 44 Operated Malignant Ulcers  
Mortality Statistics\*

MORTALITY	CASES		CAUSE OF DEATH
	Number	Per cent	
Total hospital.....	5	11.1	Coronary disease..... 2 Carcinomatosis..... 1
Total operative.....	2	4.5	Pulmonary embolus..... 1 Peritonitis..... 1

\* No death occurred in resected cases.

TABLE 6  
600 Cases of *Gastric Ulcer*  
Analysis of 44 Operated Malignant Ulcers  
Survival Period of 33 Resectable Cases

DURATION	CASES	
	Number	Per cent
2 years postoperatively.....	19	57.5
5 years postoperatively*.....	5	15.1

\* 1 patient was alive and well nine years after operation for lymphosarcoma.

#### BENIGN OPERATED GASTRIC ULCERS—211 CASES

The group of 541 benign ulcers is subdivided in our study into 330 cases treated medically and proved benign only by the patient's clinical course and roentgen findings, and those 211 cases proved benign by pathologic examination after resection.

Of the 211 patients with benign ulcer who had a resection 3 had total gastrectomy and 208 had partial gastrectomy (Table 7).

The indications for operation are given in Table 8. From this it may be seen that 89 patients, or 42.1 per cent, of this group of 211 were operated on because of the diagnosis of malignancy or because malignancy was strongly

TABLE 7  
*600 Cases of Gastric Ulcer*  
*Analysis of 541 Benign Cases*  
*Treatment of Cases*

	CASES
Operated.....	211
Total gastrectomy.....	3
Partial gastrectomy.....	208
Nonoperated.....	330

TABLE 8  
*600 Cases of Gastric Ulcer*  
*Analysis of 211 Operated Benign Ulcers*  
*Indications for Operation*

	CASES
Diagnosis of carcinoma.....	15
Diagnosis of probable carcinoma.....	74
Recurrence.....	70
Obstruction.....	17
Hemorrhage.....	3
Intractability.....	9
Failure to heal.....	21
Polyp.....	1
Planned cholecystectomy (large ulcer incidental finding).....	1

TABLE 9  
*600 Cases of Gastric Ulcer*  
*Analysis of 211 Operated Benign Ulcers*  
*Length of Follow-up Preceding Operation*

DURATION	NUMBER OF CASES
1 month or less	115
1 to 2 months	26
2 to 4 months	12
4 to 6 months	10
6 to 12 months	11
1 to 2 years	6
2 to 11½ years	31

suspected. Seventy or 33.1 per cent were resected because of recurrence, 21 or 9.9 per cent because of failure to heal, 29 or 13.7 per cent because of complications. One patient had a gastric polyp and in 1 a large gastric ulcer which

had not been discovered at roentgenologic examination was found when the patient was operated on for cholelithiasis.

Table 9 shows the length of follow-up preceding operation in the 211 patients with benign gastric ulcer. One hundred forty-one, or 66.8 per cent, of the patients were operated on within two months after they were seen at the Lahey Clinic. The others underwent resection at intervals varying from two months to eleven and a half years. As in the malignant group, the majority of these patients under medical management either in or out of the hospital satisfied our criteria for the diagnosis of healed gastric ulcer before recurrence brought them again under clinic care.

TABLE 10  
*600 Cases of Gastric Ulcer*  
*Analysis of 211 Operated Benign Ulcers*  
*Mortality Statistics*

MORTALITY	CASES		CAUSE OF DEATH
	Number	Per cent	
Total			
Hospital.....	10	4.7	Coronary occlusion..... 4 Cardiac failure..... 1
Operative.....	5	2.4	Bronchopneumonia (1932)..... 1 Peritonitis and subdiaphragmatic abscess (1933)..... 1 Pulmonary embolus (1935, 1945).... 2 Cachexia (1936)..... 1

The mortality statistics for the 211 resected benign cases are shown in Table 10. Ten of these patients died before leaving the hospital. Five, or 2.4 per cent, may be considered to have died as the direct result of the operation. The date of these deaths is included with the thought that some of them at least would not be fatalities in more recent years because of the improvements in operative technics, preoperative and postoperative care and the availability of the antibiotics.

Tables 11 and 12 show the follow-up of the 211 benign operated cases. In addition to the length of time during which varying proportions of this group were followed we have attempted to give an approximation of their status during the postoperative period into which they fall by classifying them as poor, fair or good. This estimation is based upon such factors as failure to gain weight, weakness, fatigability and anemia, as well as gastrointestinal symptoms. Although this cannot be more than an approximation, it does give some indication of the fact that as the time lengthens after gastric resection the patient is

able to adapt himself progressively both psychologically and physiologically to his altered state. Only 1 of the entire group followed had what he considered to be a recurrence of his preoperative symptoms. Roentgenograms of the gastrointestinal tract in this patient failed to show any abnormality.

TABLE 11  
*600 Cases of Gastric Ulcer*  
*Analysis of 211 Operated Benign Ulcers*  
*Follow-up of Cases*

FOLLOW-UP	TOTAL NUMBER OF CASES	CLASSIFICATION OF RESULTS		
		Poor	Fair	Good
Died in hospital.....	10	—	—	—
No follow-up.....	34	—	—	—
Less than 2 years.....	70*	5	7	58
2 to 5 years.....	51**	0	9	42
5 years or more.....	46†	0	7	39

\* 1 patient died of carcinoma of the lung in four months.

\*\* 6 patients died; 4 of cardiac disease; 1 of carcinoma of the lung; 1 of carcinoma of the pancreas.

† 1 patient died of vascular disease.

TABLE 12  
*600 Cases of Gastric Ulcer*  
*Analysis of Postoperative Symptoms and Signs in 211 Benign Operated Cases*

SYMPTOMS AND SIGNS	DURATION OF FOLLOW-UP					
	Less than 2 years		2 to 5 years		5 years and over	
	Total no.	Per cent	Total no.	Per cent	Total no.	Per cent
Dumping syndrome.....	6	8.6	3	5.9	2	4.3
Nausea and/or vomiting.....	10	14.3	4	7.8	3	6.5
Heartburn.....	5	7.1	3	5.9	2	4.3
Postprandial fullness.....	4	5.7	6	11.7	2	4.3
Fatigue and weakness.....	5	7.1	4	7.8	2	4.3
Failure to gain weight.....	8	11.4	5	9.8	10	21.7
Anemia*.....	3	4.3	10	19.3	9	19.5
Acid present.....	4	5.7	6	11.7	2	4.3
Total cases followed.....	70		51		46	

\* Hypochromic or normochromic, mild in all cases.

In this group 8 patients have died of known causes unrelated to the stomach so that the deaths did not have a bearing on the classification of their post-operative status.

#### MEDICALLY MANAGED BENIGN GASTRIC ULCERS—332 CASES

The group of gastric ulcers considered benign and treated medically (Table 13) includes 2 patients with malignant ulcer proved by postmortem examination

six and twenty-three years after they were first seen at the Lahey Clinic. These have been cited in Table 1 in the group of proved malignancies.

Of the 330 patients remaining, 41 had no follow-up after their original diagnosis. One hundred and four were followed for less than two years. Of this group 15 have died of known causes. These include 5 patients who died in the hospital: 2 after continued hemorrhage following attempts to ligate an artery in the ulcer bed; 1 of pulmonary embolus following repair of a perforation and 2 following surgery on other areas in the gastrointestinal tract. Five died of cardiovascular renal disease. Two died of hemorrhage—1 of these patients had a duodenal ulcer and the other had had a recent protracted hospital stay during which multiple complications precluded surgical inter-

TABLE 13  
*600 Cases of Gastric Ulcer*  
*Analysis of 332 Cases Diagnosed as Benign and Treated Medically*  
*Incidence of Malignancy*

LENGTH OF FOLLOW-UP	TOTAL NUMBER OF CASES	NUMBER OF MALIGNANCIES	DEATHS	
			Cause Known	Cause Unknown
No follow-up.....	41	—	—	—
Less than 2 years only.....	104	0	15	3*
2 to 5 years only.....	76	0	6	8**
5 years or more.....	111 (33.4%)	2 (1.8%)	5†	4*** (3.6%)
Total.....	332	2	26	15

† Includes 2 patients who died with malignant ulcers.

\* Ages 45, 52, 76.

\*\* Ages 30, 54, 55, 55, 64, 73, 77, 84.

\*\*\* Ages 54, 58, 67, 77.

vention. One each died of the following diseases: bladder tumor, uremia and primary carcinoma of the lung. In addition there were 3 who died of unknown causes at age 45, 52 and 76 years.

Of the patients who were followed from two to five years, 6 died from known causes; 3 of cardiovascular disease, 1 patient of streptococcus infection of the throat; 1 of uremia and 1 patient aged 65 with a duodenal ulcer of massive hemorrhage. Eight of the 76 patients followed from two to five years died of unknown causes. They were 30, 54, 55, 55, 64, 73, 77 and 84 years of age at the time of death.

One hundred eleven patients, 33.4 per cent of the 332 patients managed medically, were followed for more than five years. Eighteen were followed for ten to fifteen years, 8 for fifteen to twenty years and 2 more than twenty years. In this group 7 patients in addition to the 2 with proved malignant ulcers have died. Three died of cardiovascular disease. Four died of unknown causes at age 54, 58, 67 and 77.

If in attempting to estimate the incidence of malignant disease in the group of 111 patients followed for five years or more we assume hypothetically that all of the deaths from unknown causes in addition to the 2 proved cases were due to malignancy, the incidence of malignancy is 5.4 per cent.

TABLE 14  
*600 Cases of Gastric Ulcer*  
*Analysis of 332 Cases Diagnosed as Benign and Treated Medically*  
*Incidence of Recurrence*

LENGTH OF FOLLOW-UP	TOTAL GROUP				GROUP WITHOUT DUODENAL ULCER		
	Total Number of Cases	Number Diagnosed by X-ray	Number Diagnosed by Symptoms and X-ray	Recurrence, Per cent	Total Number of Cases	Recurrence Number	Recurrence Per cent
No follow-up.....	41	—	—	—	—	—	—
Less than 2 years.....	104	4	21	20.1	87	15	17.2
2 to 5 years.....	76	8	24	31.4	71	19	26.7
5 years or more.....	111	19	52	46.8	98	40	40.8
Total number with follow-up.	291	31	97	33.3	256	74	28.9

TABLE 15  
*600 Cases of Gastric Ulcer*  
*Analysis of 97 Patients with Recurrence Who Did Not Have Surgical Intervention*

	CASES
Did not return at time of recurrence.....	31
Refused operation.....	14
Had complicating diseases.....	13
Had a single recurrence with rapid recovery.....	10
Refused hospitalization.....	6
Aged.....	6
Severe psychoneurosis.....	3
Morphine addiction.....	1
Unexplained.....	13

In Table 14 the number of recurrences in each of the groups in which a follow-up was obtained is shown. This has been given as the total number of patients, those without duodenal ulcer and those in whom roentgenologic evidence of recurrence was obtained. It was considered important to note the presence of duodenal ulcers since the roentgenologic evidence for recurrence accounted for only 10.7 per cent of the cases with follow-up. Since it is impossible accurately to place a lesion by symptoms alone, it is probable that

some of the reported recurrences arose from activity in an associated duodenal ulcer when this was present. It is of interest to note that in gastric ulcer as in duodenal and jejunal ulcer the percentage of recurrences rises steadily as the time of follow-up lengthens.

Since recurrence is considered an indication for operation, in Table 15 we have attempted to analyze the findings in this group of 97 patients who were not operated upon. From the records of 13 of these patients no explanation could be found. The precipitation of recurrences is a point of great interest in all types of peptic ulcer. In the 97 patients with recurrence in the group of benign nonoperated gastric ulcers, the suspected causes are given in Table 16.

TABLE 16  
600 Cases of Gastric Ulcer  
*Suspected Cause of Recurrence in 97 Benign Nonresected Cases*

	CASES
Dietary indiscretions.....	7
Illness or death in family.....	5
Unrelated disease.....	1
Morphine addiction.....	1
Overwork.....	2
Worry and tension.....	4
Continuation or resumption of smoking.....	77

#### COMPARISON OF BENIGN AND MALIGNANT ULCERS

The location of the ulcers is given in Figures 2 and 3. In Figure 4 the percentage of malignant ulcers occurring in each location is presented. This percentage was arrived at by dividing the number of proved malignant ulcers in each location by the total number of proved ulcers in each location.

In Table 17 the free acid determinations in the proved cases of benign and malignant ulcers are shown. As might be expected, anacidity occurs almost twice as frequently in the malignant as in the benign group. It is demonstrated here, as well as generally recognized, that hyperacidity is not incompatible with gastric malignancy.

Table 18 compares the amount of weight loss in the total group of benign and malignant ulcers. Contrary to what might be expected, marked weight loss occurred in a far greater percentage of the benign than in the malignant group.

Table 19 shows the incidence of hemorrhage and obstruction to be similar in the benign and malignant ulcer. Perforation occurred twice as often in the benign as in the malignant ulcer.

Table 20 gives the incidence of cholelithiasis, hour-glass deformity and x-ray deformity of the duodenum found in the study. The number of patients with

cholelithiasis is approximately the finding in the population at large. The finding of hour-glass deformity in patients with gastric ulcer is of interest because of the preponderance in the malignant group. Two of the 6 in this

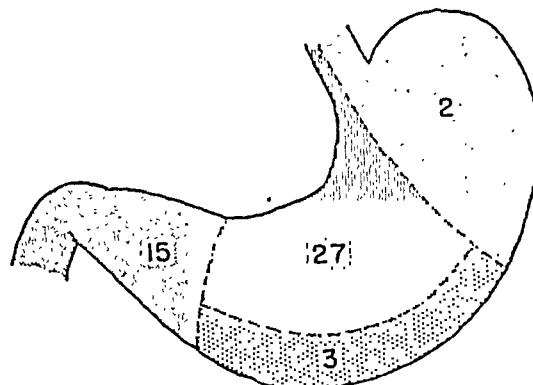


FIG. 2. 47 PROVED MALIGNANT ULCERS

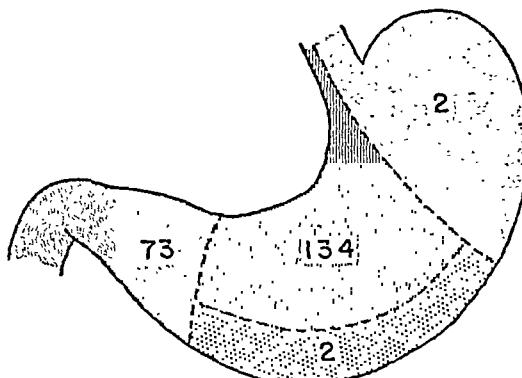


FIG. 3. 211 PROVED BENIGN ULCERS

TABLE 17

*600 Cases of Gastric Ulcer*

*Comparison of Gastric Acidity in 47 Proved Malignant Ulcers and 211 Proved Benign Ulcers*

ACIDITY	PROVED MALIGNANT CASES (47)		PROVED BENIGN CASES (211)	
	Total no.	Per cent	Total no.	Per cent
Anacidity.....	6	12.8	14	6.7
Less than 25 units.....	14	29.8	75	35.5
26 to 50 units.....	12	25.5	67	31.7
51 units and over.....	10	21.2	35	16.5
Not recorded.....	5	10.6	20	9.4

group were males. X-ray deformity of the duodenum is comparable in the benign and malignant groups.

Table 21 lists the presenting symptoms of both benign and malignant cases. Night pain was more common in the malignant than in the benign cases and

TABLE 18  
600 Cases of Gastric Ulcer  
Comparison of Weight Loss in 59 Malignant Ulcers and 541 Benign Ulcers

WEIGHT LOSS	MALIGNANT CASES (59)		BENIGN CASES (541)	
	Total no.	Per cent	Total no.	Per cent
10 pounds or less.....	10	16.9	70	12.9
11 to 20 pounds.....	13	22.0	111	20.5
21 to 30 pounds.....	5	8.4	55	10.1
31 pounds or over.....	.2	3.3	52	9.6

TABLE 19  
600 Cases of Gastric Ulcer  
Comparison of Complications in 59 Malignant Ulcers and 541 Benign Ulcers

COMPLICATIONS	MALIGNANT CASES (59)		BENIGN CASES (541)	
	Total no.	Per cent	Total no.	Per cent
Hemorrhage.....	17	29	144	26
Obstruction.....	14	24	108	20
Perforation.....	2	3	36	7

TABLE 20  
600 Cases of Gastric Ulcer  
Associated Findings in 59 Malignant Ulcers and 541 Benign Ulcers

ASSOCIATED FINDING	MALIGNANT CASES (59)		BENIGN CASES (541)	
	Total no.	Per cent	Total no.	Per cent
Cholelithiasis.....	2	3.3	28	5.1
Hour-glass deformity.....	6	10.1	35	6.4
Associated x-ray deformity of duodenum..	18	30.5	157	29.0

TABLE 21  
600 Cases of Gastric Ulcer  
Comparison of Presenting Symptoms in 59 Malignant Ulcers and 541 Benign Ulcers

PRESENTING SYMPTOMS	MALIGNANT CASES (59)		BENIGN CASES (541)	
	Total no.	Per cent	Total no.	Per cent
Epigastric postcibal pain.....	41	69.4	349	64.5
Night pain.....	25	42.2	136	25.5
Vomiting.....	12	20.3	111	20.5
Anorexia.....	9	15.2	77	14.2
Nausea.....	4	6.8	75	13.8
Abdominal pain, nonepigastric.....	13	22.0	101	18.6
Heartburn.....	5	8.4	32	5.9
Back pain.....	2	3.3	51	9.4
No pain.....	3	5.0	20	3.7

nausea more frequent in benign than malignant cases. Otherwise the symptoms were similar in both types of cases as would be expected. The variety of symptoms again emphasizes the need for careful study in individuals with any form of indigestion.

Two patients followed for twenty and twenty-three years, respectively, have special interest.

The first, a male aged 63 years, when first seen in 1928, had a short history of ulcer symptoms somewhat suggestive of carcinoma of the stomach. His ulcer was a very large lesser curvature saddle lesion, with no demonstrated evidence of duodenal ulcer. He made a rapid recovery both clinically and by roentgen examination, never had a recurrence, and died in February 1948, at the age of 83 years, of "natural causes."

The second case, a woman aged 52, when first seen in November 1924, had a very large saddle ulcer of the lesser curvature and a duodenal defect. There was a history of ulcer distress for thirty-five years and recent massive hemorrhage. There was a high range of gastric acidity. The large gastric ulcer healed completely. She had no recurrence from 1924 to 1946 or 1947 (twenty-two or twenty-three years). Cholecystectomy was carried out for gallstones in November 1937 at which time a careful search by the surgeon revealed no evidence of a scar of the gastric ulcer. In 1944, patient (aged 72 years) had cerebral arteriosclerosis and probable cerebral hemorrhage, with marked deterioration of the mental status. She was in the custodial care of the family who observed that beginning in August 1946 the patient refused all foods which were not white limiting her diet to milk, vanilla ice cream and creamed foods. By January 1947 she was taking 2 to 3 quarts of milk and cream daily. In August 1947 the patient was obviously having epigastric pain which was relieved by warm milk, and in September 1947, three weeks before death, she vomited coffee ground material. This patient died on October 18, 1947 after recurrent cerebral hemorrhage.

Postmortem findings in the stomach were as follows: specimen consisted of a stomach and 8 cm. segment of attached duodenum. The serosa was smooth. The lesser curvature fat was firmly adherent about 4 cm. proximal to the pylorus. On the lesser curvature 4 cm. proximal to the pylorus was a depression, 4 by 3 cm., having raised, firm but resilient borders. The base of the depression was white. Cross-sectioning revealed thickening in this region up to 1.5 cm. The fundus of the stomach had lost the usual rugose pattern and had innumerable petechial hemorrhages. The wall was very thin. No enlarged nodes were found in the lesser or greater curvature fat. The microscopic diagnosis was: carcinoma simplex with mucinous foci.

This patient probably had recurrence of symptoms at some time between August 1946, when she would take only white foods, and August 1947, when she was obviously having epigastric pain, relieved by warm milk. At postmortem examination, in October 1947, the lesion in the stomach was found to be carcinoma simplex with mucinous foci, without enlarged nodes in the lesser or greater curvature fat. The liver was described as normal. The pathologist searched carefully for any other scar which might represent the original ulcer

of 1924, but none was present. The only deduction to be drawn, therefore, is that after twenty-two or twenty-three years, this patient had a recurrence of her gastric ulcer which was immediately malignant, or became so during the fourteen months before her death.

#### DISCUSSION OF FINDINGS

The authors of this paper believe that the above study furnishes by no means final nor decisive data on the controversial point for which it was undertaken: namely, whether all gastric ulcers should be regarded as surgical and resection done. This study, we believe, should be only one of many throughout the country. It is important that there be a correlation of surgical and gastroenterologic opinion and definite policies established, so that the individual

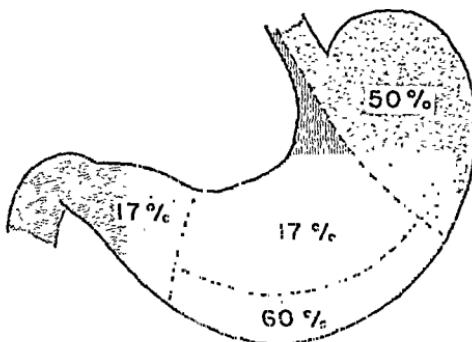


FIG. 4. INCIDENCE OF MALIGNANCY IN VARIOUS LOCATIONS

gastroenterologist and surgeon, whose experience is still insufficient for reasoned judgment may have some evidence to guide him to the correct therapy for the individual patient.

Several points of special interest have been suggested by our study: (1) The male patient is a little more than twice as prone to gastric ulcer as the female, but more than four times as prone to malignant ulcer.

In the differential diagnosis, x-ray, the history and the clinical course of the patient are our chief guides. Of these, x-ray is the most valuable and the importance of careful fluoroscopic and film examination cannot be overestimated.

(2) The symptoms are disarmingly similar in the benign and malignant cases. In a small percentage they are absent in both. In the individual case the character of the symptoms may vary so far from the classical standard as to be misleading. In our study, for example, loss of weight occurred in a larger percentage of the malignant cases only in those who had lost twenty pounds or less, while in those who had marked weight loss (thirty-one pounds or more) those with benign gastric lesions predominated almost 3 to 1.

The location of the lesion has some significance since as is shown in Figure 4

the greater curvature and fundus have the highest percentages of malignancy, 60 per cent and 50 per cent (although their total incidence is too small to be conclusive). The prepylorus and pylorus, and the corpus show an incidence of malignancy of only 17 per cent in each location in this series. It should be especially noted that less than one-fifth of the prepyloric lesions in our series were malignant. Furthermore, the same percentage of malignancy is found on the lesser curvature of the corpus. Nevertheless the greater frequency of ulcers in these regions diminishes the percentile incidence but does not change the fact that the greatest number of malignancies are to be found in these areas.

Gastroscopy (Table 22) must be regarded only as an accessory to x-ray in the differentiation of benign and malignant gastric ulcer, chiefly because of the

TABLE 22  
*Patients Who Had Gastroscopy Performed*  
124 Cases

	CASES	PER CENT
Examination unsatisfactory.....	31	25.0
Cardiospasm, hour-glass stomach, lesion in "blind spot" of instrument, lesions not visualized although present by x-ray and/or at surgery		
Lesion visualized.....	93	75.0
Diagnosed benign, confirmed by x-ray and/or surgery.....	60	64.5
Diagnosed benign and proved malignant.....	4	4.3
Diagnosed question malignant, proved benign.....	21	22.5
Diagnosed malignant and proved malignant.....	8	8.6

73.1 per cent accurate.

26.8 per cent inaccurate.

occurrence of these lesions in areas which are blind spots to the gastroscopist. In 4.3 per cent of this series of 93 cases in which the lesion was visualized a gastroscopic diagnosis alone of "benign ulcer" would have suggested a false security, and in 25 per cent of all cases gastroscoped no help at all was obtained. Table 17 shows that the dependence upon acid values is, as has long been suspected, of little significance in differential diagnosis, although the percentage of cases showing achlorhydria is greater in malignant than in benign cases. It is interesting to note that contrary to an often expressed opinion of many of us, no dependence can be placed upon the associated x-ray finding of duodenal ulcer with the gastric lesion in the differentiation of benign and malignant ulcer; in our cases, an x-ray defect of the duodenum was diagnosed in 31 per cent of those gastric ulcers which were proved malignant. This finding is now being further investigated and will be published in a separate study.

(3) In 111 cases followed from five to twenty-three years, only 2 had recurrences with malignancy (1.8 per cent of this group). Adding the 4 deaths of unknown cause to these 2 and assuming (entirely hypothetically) that these deaths were from cancer of the stomach, the percentage would still be only 5.4 of the 111 cases. Even this percentage, in part at least hypothetical, compares favorably with the hospital mortality of 4.7 per cent and operative mortality of 2.4 per cent in the 211 cases of benign ulcer resected and is appreciably lower than the usually estimated incidence, 10 per cent, of malignancy in gastric ulcer. To be sure, the latter was accumulated chiefly in earlier years when surgical and anesthesia techniques were not yet at their present optimum.

(4) The length of follow-up preceding resection in malignant gastric ulcers is the vulnerable point in our gastroenterologic experience. The mistakes made in the cases of the 20 patients (Table 4) who were carried along on medical treatment from two months to seven years, and then operated upon and found to be malignant, are not to be condoned unless, as we believe was true in certain of these cases, malignant changes occurred only with the later recurrence. In 1941, one of us (S. M. J.) called attention to evidence which seemed to indicate that such changes might occur in recurrent gastric ulcer, and since that time, this belief has been strengthened by further evidence, of which the case history quoted is a notable and striking example. Dr. Shields Warren, Pathologist at the New England Deaconess Hospital, concurs in this opinion. He believes that with the healing and recurrent breaking down process, cell changes occur which may give rise to malignancy. There is, in this respect, perhaps an analogy between gastric ulcer and chronic endocervicitis and possibly also with ulcerative colitis. These 20 cases then were obviously the individuals in this entire group of whom it is known that they might have been saved a death from cancer of the stomach from which they died, if they had been operated upon as soon as first seen. They constitute 3.3 per cent of the total group.

(5) This potentiality of the recurrent gastric ulcer to become malignant, if accepted as factual, must then be discussed in the light of this study. Our only logical conclusion regarding recurrence is that since in our opinion the recurrent gastric ulcer harbors potential malignancy, any recurrence must be an indication for resection. Our study shows that 40.8 per cent of 98 cases of gastric ulcer *unassociated* with duodenal ulcer, followed for five years or more had recurrences while 59.2 per cent did not. This indicates that about 60 per cent of those cases of gastric ulcer (without duodenal ulcer) certainly had no malignant changes in their original ulcer, and if they could be protected against recurrence they would be safe from the danger of future malignancy in the area of the original gastric ulcer and need not have their normal gastric function disturbed by resection.

The policy of resection of all recurrent ulcers will result in the resection of many benign ulcers, as indicated in Table 8 where 42 per cent of the 211 cases had resection because of a diagnosis of positive or suspected malignancy, and 33 per cent because of recurrence. However, this sacrifice must be condoned as a concession to the ultimate good and safety of the patient. Table 16, which shows the suspected causes of recurrence in benign cases is of interest because in 80 per cent of these cases, persistence or resumption of smoking was the only known impeachable factor.

(6) The question of dependence upon evidences of healing must again be discussed in the light of this study. The established criteria for healing are still valid: complete disappearance of the x-ray defect, complete subsidence of symptoms and disappearance and nonrecurrence of occult blood in the stools.

TABLE 23  
*Healing Time in Patients with Gastric Ulcer with Frequent X-rays  
(145 Cases)*

HEALING TIME	NUMBER OF CASES
1 week	4
2 weeks	19
3 weeks	32
4 weeks	29
5 weeks	17
6 weeks	13
7 weeks	7
8 weeks	15
Over 8 weeks	9

Of these three criteria, the x-ray evidence is of greatest value. By complete disappearance of the x-ray defect is meant not only the disappearance of the crater, but a complete return of flexibility in the gastric wall at the site of the ulcer and the absence of the so-called dimpling defect. Any rigidity in this area may well indicate malignant change at the base of what appears to be a healed ulcer. Complete absence of rigidity is of as much importance as the disappearance of the crater. In our study, it was found that the speed of healing was apparently not at all related to (1) the danger of recurrence; (2) the duration of symptoms and (3) the age of the patient at the time treatment was started. As stated above there were 20 cases in our series in which operation for suspected malignancy was not done within two months, but which when finally operated upon, had proved malignancy.

Our study (Table 23) shows that healing in 145 cases studied with frequent x-rays, was complete in 84 cases within four weeks—and in 52 cases between five and eight weeks. The progress of healing should be obvious in three to

four weeks, and in all cases complete within six to eight weeks. Furthermore, all other subjective and objective signs should be favorable if the case is to be continued on a medical regimen. The patient should be adequately instructed as to the nature of gastric ulcer and the potential danger of recurrence. This educational program has two purposes: (1) the complete cooperation of the patient in maintenance of healing, and (2) his immediate return for examination in case of recurrent symptoms. Upon these two factors safety in treating gastric ulcer depends. Unless there can be assurance that these measures will be carried out, resection may well be safer.

#### SUMMARY

The evidence collected in this study presents in summary, grounds for the following opinions:

- (a) That gastric ulcer, while a definitely potential origin for malignancy, is not so perilous that the patient who has it cannot be treated as an individual case, rather than by a general policy of resection of all cases.
- (b) That the first occurrence of gastric ulcer must be treated with intensity and persistence—so that proved complete healing is obtained, and absence of recurrence maintained.
- (c) That failure of complete healing, within six to eight weeks as a maximum, and all recurrences be treated as soon as possible by resection.

#### DISCUSSION

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): We are indebted to the essayists for their contribution to one of our most pressing problems. The numerous articles on the subject in the past decade are confirmation of our deep interest and concern. We are frequently asked to express our views on the differential aspects of chronic benign gastric ulcer and small ulcerating carcinoma and on what circumstances we base our decision as to the choice between immediate surgical intervention and more conservative measures. My discussion is chiefly concerned with these phases of the problem.

One could quickly dismiss the subject of differential diagnosis by saying that the only absolute proof as to the true nature of the lesion is histologic examination of serial sections and that the most reliable evidence of benignancy or carcinoma, short of histologic examination, is the effect of adequate medical treatment in hospital. The decision as to operation or treatment, in the opinion of the internist with large experience, is contingent on a number of factors, in contrast to the present day attitude of some representative, otherwise conservative surgeons, who would advocate immediate operation on every ulcerous gastric lesion.

Actually, the incidence of gastric ulcer in comparison to duodenal ulcer is strikingly less frequent (1:12.2) and one never needs to worry about the latter masquerading as carcinoma. From a roentgenologic standpoint, 10 to 12 per cent of our proved

cases of carcinomatous ulcers are indistinguishable from benign ulcers. Our surgical pathologists in recent years have pointed out the small size of ulcerating malignant lesions at the time of gastric resection. The diameter of 13.5 per cent of such lesions was 2.5 cm. or less. These facts should constantly put us on our guard, and constitute justifiable argument for surgical interference without unnecessary delay when there is any reasonable suspicion for the presence of carcinoma. In the series reported herewith by Dr. Smith I take it that 42 per cent presented symptoms or signs pointing to malignancy. Such evidence is not necessarily conclusive because in as high as 28 per cent of our own cases of benign ulcer verified at operation the summation of findings favored the diagnosis of carcinoma. So it is possible to err in both directions.

Our statistics are also in variance with another statement advanced by the essayist. Are we given to understand that one-third of the patients with carcinoma had a duodenal defect implying the presence of an active, latent, or healed duodenal ulcer? In our experience, and that of many others, the co-existence of duodenal ulcer and gastric cancer, especially in the small circumscribed form, is rare. Wilbur and Rivers pointed this out in 1932. According to Fischer, Clagett and MacDonald (1947), of the patients having duodenal ulcer seen at the Clinic only one in 938 (0.1 per cent) had a co-existent malignant gastric lesion. Gastric carcinoma is preponderantly a disease of the male sex. This fact is reflected in the data presented by the essayist as carcinomatous ulcer was four times more frequent in the male than in the female. But one should not rely too much on this aspect in differential diagnosis because both benign and malignant gastric lesions are preponderant in the male, the ratio of the former being 4.3 males to one female, from our standpoint. On the basis of an accumulated experience over many years, the features favoring malignancy of small ulcerous gastric lesions are as follows: recent onset of symptoms in elderly patient; large size of lesion; location on greater curvature or prepyloric area—to less extent on anterior or posterior wall; progressive clinical course; presence of histamine-fast achlorhydria; early pyloric obstruction; increase in size of lesion during course of adequate treatment; persistence of occult blood in feces on controlled diet; gastroscopic appearance—lesion elevated, its edges or rims blend with mucosa, the irregular floor is a brownish red, violet, gray or dirty color, perhaps containing nodules, nodes or ridges; and, the presence of Meniscus sign complex. These features, with the possible exception of the last mentioned one, are of course relative rather than absolute.

The contribution under discussion also emphasizes an added feature, namely the early recurrence of the lesion following treatment. This aspect of carcinoma has not been adequately emphasized in previous contributions and in large measure is an original observation.

DR. WALTER L. PALMER (Chicago, Ill.): Mr. President, Ladies and Gentlemen: Like Dr. Eusterman, I, too, thoroughly enjoyed this paper presented by Dr. Jordan's very charming companion. I do not wish to consider the differential diagnosis of the benign-malignant ulcer at all, but rather to speak for a moment on this subject of the relationship between benign ulcer and gastric cancer, or rather on the question as to whether benign peptic ulcer is a precursor of gastric cancer.

Of course, for many years it has been so considered. In one of the best books on cancer, "Der Magenkrebs," Georg Konjetzny discusses the subject in considerable detail, and takes the view that benign gastric ulcer and atrophic gastritis are the two precursors of gastric cancer.

I have for a number of years been interested in the literature which purports to prove that benign ulcer can undergo malignant transformation, and I must admit that I am not convinced that anyone has ever proved that to be a fact.

I am interested in the different ways in which Dr. Smith's figures can be interpreted. I would interpret her figures as conforming with the view I take, namely, that gastric ulcer is not a precursor of gastric cancer. The low incidence, as I recall it, 1.8 per cent, seems to me to be about what one would expect on the basis of coincidence because, while, as Dr. Eusterman has pointed out, and Dr. Wilbur and others have shown, gastric cancer is very rare in a stomach associated with duodenal ulcer, it is not so rare in association with gastric ulcer. I am sure that we have all seen in the same stomach independent benign and malignant lesions, so that even the story of many years of ulcer distress, twenty-three years, does not prove that the gastric ulcer had anything to do with the carcinoma which sooner or later developed in that same stomach, even though it seemed to develop at the same site, because these gastric cancers can rapidly encroach upon the benign ulcer or the gastric cancer itself undergoes peptic ulceration and then, as Dr. Eusterman has said, mimics completely in its architecture and in many other respects, the benign gastric ulcer.

There is another subject I should like to discuss, although it was not touched upon by Dr. Smith: namely, the secretion in gastric ulcer.

We consider the question settled as a result of the studies of Dr. Levin and Dr. Kirsner. Dr. Levin found that in normals, and he used nervous medical students and others, the average acid secreted at night was around 680 milligrams. Now then, in gastric ulcer, the average secretion was less than that in the normal group. This is in striking contrast with the duodenal ulcer group in which the level was three and a half times that of the normal group, so that in gastric ulcer we do not have to deal with the problem of the severe hypersecretion.

Now this is not to say that acid is of no consequence in benign gastric ulcer; in fact, we take quite the contrary view because in all patients with chronic benign gastric ulcer, one can demonstrate, if one is persistent and performs enough histamine tests, the presence of acid gastric juice.

One must admit, however, that in many patients the secretory level is very low, a free acidity of 12, 18, or 20 clinical units. Now, you may take the position that I am quibbling about such low free acid. You may say: Why not call them achlorhydrics? Why argue about 12 or 15 degrees? It is because of the very point brought out by Dr. Hollander; namely, that a free acidity of 12 or 15, shall we say, has a pH of around 3 to 3.5, quite sufficient to activate pepsin. Peptic activity can and does occur at that pH and we think it plays a most important role in the formation of benign ulcer. [Applause]

DR. THEODORE L. ALTHAUSEN (San Francisco, Calif.): (Mr. President and Members and Guests): This is one of the largest carefully analyzed series of gastric ulcers

on record, and, as Dr. Palmer said, there are various features that we can seize upon for comment.

I was interested in the fact which I have noticed also in other series that the operative mortality of gastric resection at the Lahey Clinic is equal to that of the occurrence of carcinoma in cases of gastric ulcer which had been diagnosed as being benign. At hospitals of lesser excellence this mortality undoubtedly exceeds the risk of malignancy.

In this connection it has come to my attention that indications for surgical intervention emanate from institutions where there are highly skilled surgical teams, where there is excellent preoperative preparation, where the latest methods of anesthesia are used, and where there is up-to-date post-operative care. These surgical indications are being followed by surgeons all over the country many of whom have more modest facilities and degrees of skill at their command with the result, that their mortality rates are considerably higher.

This is a delicate point but it seems to me that until surgical facilities and skill are much more standardized than they are at present indications for surgical intervention in various diseases should be on a sliding scale becoming more conservative as the surgical mortality for a given hospital or surgeon increases above that of the recognized leaders.

DR. SARA M. JORDAN (Boston, Mass.): I want to say first that there is a great deal of material in the paper which couldn't be given because of lack of time. The point that Dr. Eusterman made about the association of benign gastric ulcer with duodenal ulcer, is one of them. That point I must say I was very much surprised about, when I saw the results of our study. I had assumed, as I think most of us have, that to have a duodenal ulcer in association with a gastric ulcer was pretty good security against malignancy of the gastric ulcer, and that we need not worry about the possibility of that gastric ulcer becoming malignant; but in our cases, 29 per cent malignant gastric ulcers also had an X-ray defect in the duodenum. We are going to make this point the subject of a special study of more cases.

Our study we regard simply as a stimulus, and we hope the rest of the country will follow along with more intensive research on all their gastric ulcers, because we regard this as a very important issue toward reasonable correlation of gastroenterology and surgery in the treatment of gastric ulcer.

Our evidence collected in this study presents grounds for the following opinions, we believe:

First, that gastric ulcer, while a definitely potential origin for malignancy, is not so perilous that the patient who has it cannot be treated as an individual case rather than by a general policy of resection of all cases.

Secondly, that the first occurrence of gastric ulcer must be treated with intensity and persistence so that proved complete healing is obtained, and here I should like briefly to mention the fact that no roentgenological "dimple" can be regarded as harmless. In other words, the gastric wall must be completely flexible. That is an important point, we believe, and we must also be sure that an absence of recurrence

is maintained. In our paper, we have evidence, we believe, that a transformation from a benign to malignant character takes place as time goes on in a certain small group of these cases.

Finally, failure of complete healing within six to eight weeks as a maximum, and all recurrences must be treated as soon as possible by resection.

I should like just a minute to show two slides.

(Slide) This one is a case I have talked a great deal about, a woman we saw in 1924. There is an advantage in getting old. We know something about our long-followed cases.

(Slide) This woman had that large gastric lesion, as you see, very large, on the lesser curvature, with a history indicated here. She was fifty-two at that time, and we followed her along through the years until 1944, when it was impossible to X-ray her again because she had cerebral disease, cerebral arteriosclerosis and occasional hemorrhages, and was mentally unable to be brought to the Clinic. She was under custodial care by her family.

Now, in the three years that followed between 1944 and 1947—in February, 1947, she began to take only white food. She would take nothing but milk, and ice cream, anything that was white. In June 1947, she showed definite evidence of epigastric pain, which was relieved by milk, and she took very large quantities of it all day long.

In October, she died of another cerebral accident. I might mention that in 1937, that is, ten years before she died, she had a gallbladder with stones, for which Doctor Lahey operated, took out the gallbladder, and at that time he had an opportunity to look the stomach over very carefully, and could find no evidence of that scar of the gastric ulcer.

In October 1947, when she died, the stomach was immediately examined by our pathologist, with the following interesting findings. He could find no evidence of any scar tissue on the lesser curvature side, or anywhere in the stomach. He did find, however, in the area which he designated as the site of this ulcer twenty-three years previously, a lesion which he, on microscopic examination, found to be carcinoma. When he first examined it, he thought it was an ulcer. On histological examination, he found it to be a carcinoma.

Now that case, I think, must indicate that a recurrence occurred and malignant changes took place.

Contrary to that case, or in comparison with that case, we have another one who was followed for twenty years and just died, and therefore his ulcer history has ended. He had, again, one of these large saddle ulcers of the lesser curvature, no recurrence during the twenty years, and he died in February of this year of what was called "natural causes," at the age of eighty-three.

These two cases, I think, are extremely interesting, one showing the transformation, and the other without pathological evidence, to be sure, indicating that there had been no recurrence of gastric ulcer.

## OBSERVATIONS ON THE EXCESSIVE NOCTURNAL GASTRIC SECRETION IN PATIENTS WITH DUODENAL ULCER\*

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### INTRODUCTION

It is now generally accepted that the formation of peptic ulcer is dependent upon the presence of acid gastric juice<sup>1-2</sup>. Experience has shown, furthermore, that the continued excessive secretion of hydrochloric acid retards healing, whereas a decrease or complete elimination of acid promotes healing of the ulcer<sup>3</sup>. The difficulty in controlling the nocturnal gastric secretion may be the most important problem in therapy<sup>1-7</sup>. The presence of an excessive continued night secretion in patients with duodenal ulcer has been demonstrated<sup>8</sup>; thus, the average volume and output of hydrochloric acid in the twelve hour night secretion of 32 patients with duodenal ulcer measured 1004 cc. and 2242 mg. respectively, as compared with 581 cc. and 661 mg. in a group of 33 normal persons.

The purpose of the present report is (a) to describe five patients with either recurrent or "intractable" ulcer in whom the nocturnal gastric secretion exceeded the average for individuals with duodenal ulcer, and (b) to indicate the difficulty sometimes encountered in effectively reducing this hypersecretion.

### CASE HISTORIES

*Case 1.* W. R. (Unit No. 422717), (Table 1, Fig. 1), a 43 year old male foreman, with episodes of severe gnawing epigastric pain of five years' duration, was admitted to the surgical service of the Billings Hospital on December 12, 1947. The pain was not relieved by morphine in doses of 0.030 to 0.045 grams daily. X-rays disclosed a deformity of the duodenal bulb with a centrally located crater. The patient was transferred to the gastrointestinal service for treatment. The maximum free acidity after histamine stimulation was 103 clinical units. Two aspirations of the twelve hour night secretion (8:30 p.m.-8:30 a.m.) yielded 4404 and 3237 mg. of hydrochloric acid. On December 23 and 24, the stomach was aspirated continuously day and night. The output of acid remained excessive despite the administration of large amounts of atropine, and 5000 mg. of an enterogastrone concentrate given intramuscularly in a single injection. Huge quantities of alkali were required to relieve the ulcer pain, the patient receiving, during a period of 23 days, 1066 grams of calcium carbonate, 114 grams of magnesium carbonate and 206 grams of sodium bicarbonate; two milligrams of atropine were given in the evening. In addition, the stomach was lavaged with a solution of sodium bicarbonate. From December 27, 1947 to January

\* Presented at the Annual Meeting of the American Gastroenterological Association, Atlantic City, N. J., May 1, 1948.

NOCTURNAL GASTRIC SECRETION(HCL MG.) AND COURSE OF PEPTIC ULCER  
W.R.-422717-MALE-AGE 43-DUODENAL ULCER, 5 YEARS DURATION

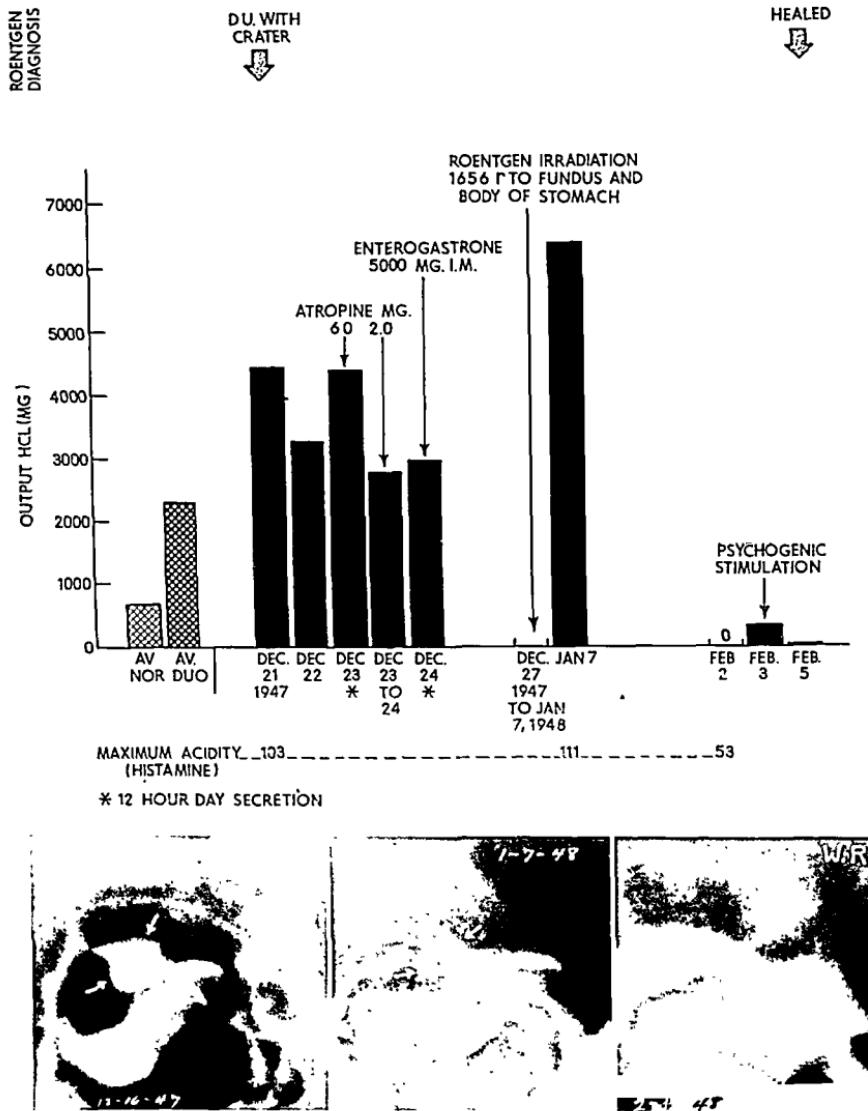


FIG. 1

7, 1948, roentgen irradiation, with a total dose of 1656 r, was directed to the fundus and body of the stomach in an attempt to reduce gastric acidity. The twelve hour nocturnal secretion at the conclusion of irradiation contained the enormous amount

of 6353 mg. of hydrochloric acid, nearly three times larger than the average for duodenal ulcer. The maximum acidity (histamine) was 111 units. However, on medical management, the ulcer pain subsided and the patient left the hospital on January 9, 1948.

He remained well, but returned on February 2, 1948, for further study. The free acidity (histamine), a month after the completion of radiation therapy, now reached a maximum of only 53. The initial twelve hour nocturnal aspiration (Feb. 2) yielded 690 cc. with no free acid. The following evening the patient was purposefully informed that, contrary to the anticipated three days of hospitalization, he must remain for several weeks and receive painful injections daily. He became extremely resentful and cried profusely. Free hydrochloric acid appeared in the gastric content

TABLE 1  
*Twelve Hour Nocturnal Gastric Secretion in Case 1 (W. R.)*

DATE	VOLUME	FREE HCl	TOTAL OUTPUT HCl	COMMENT
Dec. 21, 1947	2200	55	4404	
Dec. 22	1305	68	3237	
*Dec. 23.	1544	77	4344	Atropine 6.0 mg.
Dec. 23-24	1486	54	2749	Atropine 2.0 mg.
*Dec. 24	1429	56	2924	5000 mg. Enterogastrone at 1:30 p.m.
Dec. 27, 1947-Jan. 7, 1948	Roentgen irradiation—1656 r (depth dose) to fundus and body of stomach			
Jan. 7, 1948	2184	80	6353	
Feb. 2	690	0	0	26 days after X-ray therapy
Feb. 3	759	11	297	Psychogenic stimulus
Feb. 5	621	<1.0	13	

\* 12 hour day secretion (8:30 a.m.-8:30 p.m.).

until 12:30 a.m.; the patient then fell asleep and the remaining hourly specimens contained no acid. The twelve hour secretion measured 759 cc. with 11 units of acid, a total output of 297 mg. of HCl, produced during the first four hours of the period. The patient was reassured on the following day that there had been an error and that he would return home as originally planned. On February 5, the twelve hour aspiration yielded only 13 mg. of hydrochloric acid. Roentgen study demonstrated healing of the ulcer and the patient was dismissed from the hospital.

#### COMMENT

The intense ulcer pain, not relieved by large quantities of morphine, subsided only after repeated gastric aspiration and the administration of 60 grams of alkali daily. The output of hydrochloric acid in the twelve hour nocturnal gastric secretion ranged from 3237 to 6353 mg., approximating an average of 3820 mg., considerably larger than the mean for duodenal ulcer. It remained high during the administration of

atropine and enterogastrone. The relationship between the tremendous secretion of hydrochloric acid and the intense, almost uncontrollable, pain seemed to be quite direct. Roentgen irradiation to date has very effectively reduced the secretion, and thereby facilitated healing of the ulcer.

The temporary increase in acid output following deliberately induced resentment and anxiety coincides with the results of a similar experiment reported elsewhere<sup>9</sup>.

*Case 2.* E. R. (Unit No. 365798) (Table 2, Fig. 2), a 49 year old male accountant, had experienced recurrent ulcer distress, complicated by five massive hemorrhages, since 1930. He first appeared at the University Clinics in September 1945. X-rays

TABLE 2  
*Twelve Hour Nocturnal Gastric Secretion in Case 2 (E. R.)*

DATE	VOLUME	FREE HCl	OUTPUT HCl	COMMENT
	cc.	Ci. Units	mg.	
Oct. 3, 1945	1800	65	4259	
Oct. 4	1700	55	3403	
Oct. 5	1650	62	3724	
Oct. 5-19				Roentgen irradiation, 1647 r (depth dose) to fundus and body of stomach
Nov. 1	245	18	160	14 days after X-ray therapy
Nov. 2	315	9	103	
Jan. 19, 1946	1000	25	910	
Jan. 20	1200	23	1004	112 days after X-ray therapy
June 22	1600	48	2795	
June 23	1560	57	3287	
March 3, 1947	1623	64	3782	
July 3	711	47	1224	
July 5	907	78	2588	Enterogastrone 3000 mg.
Aug. 26	1186	48	2076	Atropine 3.0 mg.
Aug. 27	897	55	1786	Atropine 6.0 mg.
Aug. 31	1179	57	2441	
Sept. 2				Transabdominal Vagotomy—Posterior Gastroenterostomy

revealed an ulcer crater in a deformed and moderately stenosed duodenal bulb. The maximum free acidity (histamine) was 108 clinical units. The output of hydrochloric acid in the twelve hour nocturnal period ranged from 3403 to 4259 mg. Roentgen irradiation, 1647 r (depth dose), was directed to the gastric fundus during the period October 5 to 19, 1945. Standard antacid therapy was continued; the patient improved rapidly and he left the hospital within two weeks. Two weeks after the irradiation, the nocturnal output of acid decreased to 160 and 103 mg. in two successive periods. The free acidity (histamine) now reached a maximum of only 35. Three months later 910 and 1004 mg. were aspirated during the night.

The patient remained well until June 1946 when he again entered the hospital because of recurrent ulcer distress. The nocturnal secretion now contained 2795 and 3287 mg. of hydrochloric acid. Roentgen study disclosed a large ulcer crater in

a moderately deformed duodenal bulb. Antacid therapy was continued and healing of the ulcer was observed radiologically on September 27, 1946; there was, however, marked stenosis of the duodenum. The maximum acidity (histamine) ranged from

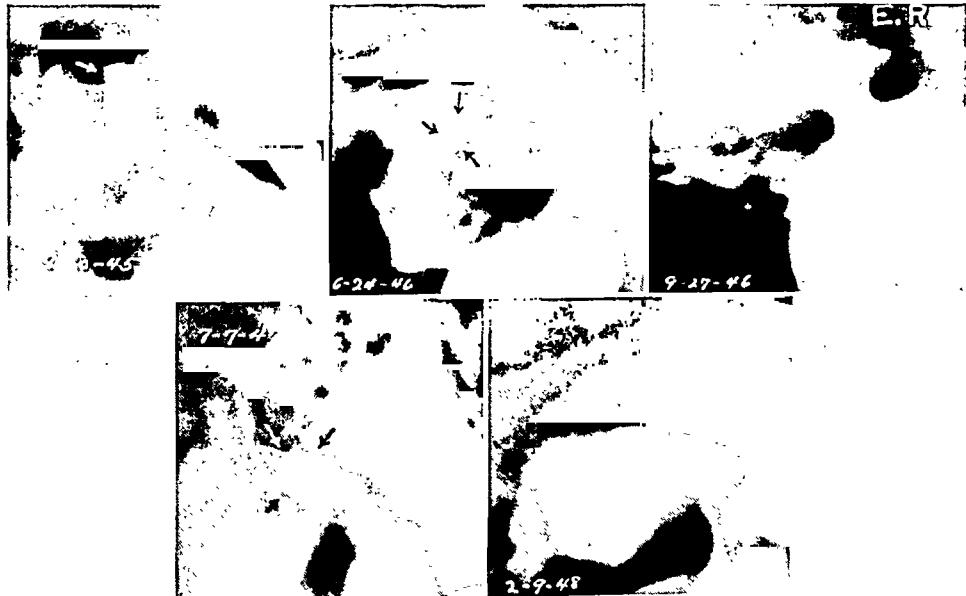
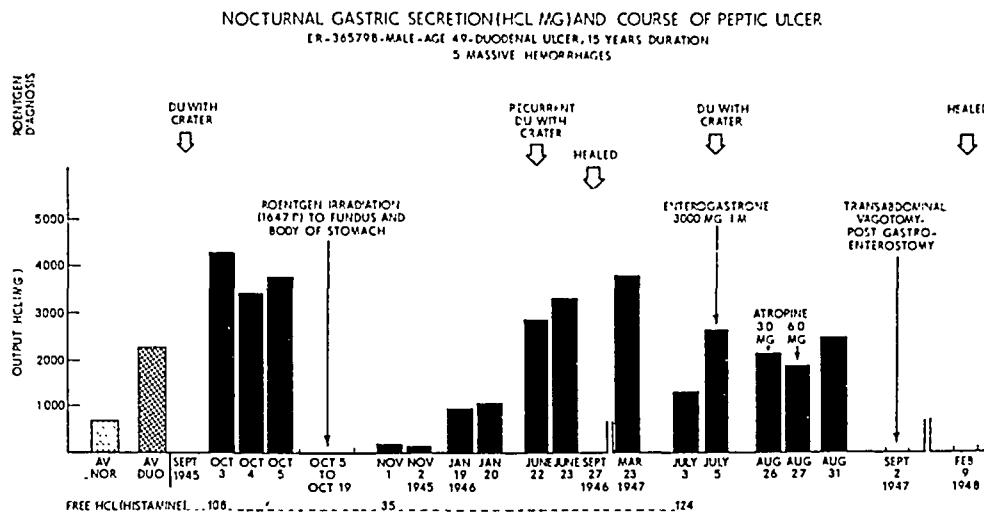


FIG. 2

73 to 105 units. On March 23, 1947, the twelve hour nocturnal secretion contained 3782 mg. of hydrochloric acid.

Three thousand mg. of an enterogastrone concentrate, administered intramuscularly in five divided doses each of 600 mg. on July 5, 1947, had no apparent effect.

The free acid during a continuous histamine test rose to 124 and was not reduced by the single intramuscular injection of 1000 mg. of enterogastrone. Roentgen examination demonstrated an ulcer crater in a moderately deformed duodenal bulb. Gastric secretion remained high despite the subcutaneous administration of atropine, in doses of 3.0 and 6.0 mg. in twelve hours.

A transabdominal vagotomy and posterior gastroenterostomy were performed on September 2, 1947, with uneventful recovery. The patient has remained well to the present time. (Aug. 1948) An attempt was made to measure the nocturnal gastric secretion on February 7 and 8, 1948; volumes of 246 and 486 cc. were aspirated with average free acidities of 10 and 26 units respectively; however, values of 18 and 55 units were obtained on individual specimens. Since the collections were inaccurate, due to the reflux of intestinal content through the gastroenterostomy, these data are not recorded. The insulin test was positive.

#### COMMENT

Recurrent ulcer distress had been experienced for 17 years, complicated by five massive hemorrhages. The output of HCl in the nocturnal secretion approximated an average of 3795 mg., considerably larger than the mean for patients with duodenal ulcer. Roentgen irradiation lowered gastric secretion for 8 months during which time the ulcer healed and the patient remained without symptoms. The output of hydrochloric acid then returned to the original levels; it was not reduced significantly by atropine, up to 6.0 mg. in twelve hours nor by an enterogastrone concentrate<sup>10</sup>. In this instance again, a recalcitrant duodenal ulcer occurred in association with a tremendous fasting gastric secretion. Reduction of the secretion temporarily by radiation was followed by healing of the ulcer. The ulcer later healed again after vagotomy and gastroenterostomy<sup>11</sup>, an excellent result being obtained in spite of a positive insulin test.

*Case 3.* A. J. (Unit No. 255356) (Table 3, Fig. 3), a 43 year old male photoengraver, first experienced upper abdominal discomfort in January 1940. Nausea, vomiting and dull epigastric pain appeared several months later. An operation, performed elsewhere, was reported to have disclosed an inoperable carcinoma of the pancreas. A severe, constant pain subsequently developed across the back and was not relieved by analgesics, sedatives or opiates. Additional symptoms included anorexia and a loss of approximately 44 pounds in weight. He was referred to the Billings Hospital on January 10, 1941 for a chordotomy to relieve the intense pain presumed to arise from a carcinoma of the pancreas. The pain persisted despite the administration of large quantities of aspirin, codein and morphine. Roentgen examination revealed a duodenal ulcer crater. Two gastric analyses (histamine) yielded maximum free acidities of 108 and 117 clinical units. The back pain was reproduced almost immediately by the introduction of 200 cc. of 0.5 per cent hydrochloric acid into the stomach and was promptly relieved by aspiration of the gastric content. Two measurements of the twelve hour nocturnal secretion yielded 2498 and 3243 mg. of acid, despite the administration of 2.0 mg. of atropine during each period. The

pain subsided following antacid therapy and nightly aspirations; a total of 2,394 grams of calcium carbonate and 276 grams of magnesium carbonate were administered during a period of 48 days and atropine was given orally in doses approximating 8 milligrams daily. Roentgen irradiation, 1169 r (total depth dose), was directed to the fundus of the stomach between February 4 and February 14, 1941. The maximum acid response (histamine) decreased within several weeks to 70 clinical units, increased one month later to 90, and subsequently varied from 94 to 109 units. Healing of the ulcer was observed roentgenologically on March 24, 1941. The maximum

TABLE 3  
*Twelve Hour Nocturnal Gastric Secretion in Case 3 (A. J.)*

DATE	VOLUME	FREE HCl cc.	Cl. Units	OUTPUT HCl mg.	COMMENT
Feb. 5, 1941	1400	49	2498	Atropine 1.0 mg.	
Feb. 6	1100	81	3243	Atropine 1.0 mg.	
Feb. 14-24					Roentgen irradiation 1169 r (depth dose) to fundus and body of stomach. No immediate post-radiation studies of gastric secretion.
Dec. 14, 1943	1300	62	2934		
Dec. 15	1000	94	3422		
Dec. 20	1090	50	1984		
Dec. 21	1300	55	2603		
Jan. 19, 1944					Roentgen irradiation, 1380 r (depth dose) to fundus and body of stomach
April 30	2000	34	2476	Atropine 1.0 mg.	
May 3	1300	60	2839	Atropine 1.0 mg.	
May 4	1225	52	2319	Atropine 1.0 mg.	
May 8					Transthoracic Vagotomy
May 20	530	30	579		
May 21	130	0	0		
May 22	400	32	466		
*June 18	640	20	466	Atropine 2.0 mg.	
July 1	785	36	1028		
July 3					Gastroenterostomy for obstruction. No evidence of active ulcer. Insulin test positive.

\* 9 hours.

acidity during 1942 and 1943 ranged from 95 to 128, usually exceeding 110 units. Roentgen examination indicated deformity of the duodenal bulb, but no crater.

The ulcer recurred in November 1943, despite the use of 4.0 grams of calcium carbonate hourly and approximately 8.0 milligrams of atropine daily. The nocturnal output of acid ranged from 1984 to 3422 mg. The symptoms were controlled by antacid therapy; X-ray examination subsequently indicated healing of the ulcer. An additional 1380 r (depth dose) were directed to the gastric fundus between January 3 and January 19, 1944; the output of acid decreasing slightly.

Ulcer pain recurred occasionally during the next three months. The patient re-entered the hospital on April 27, 1944, because of increased pain in the upper abdo-

men and vomiting of 12 hours' duration. The twelve hour night secretion contained from 2319 to 2839 mg. of hydrochloric acid.

A transthoracic vagotomy was performed on May 8, 1944, with a subsequent marked reduction in gastric secretion to approximately normal levels. The patient left the hospital two weeks after operation, but was readmitted three weeks later because of anorexia, nausea, vomiting, and vague epigastric discomfort. Roentgen examination demonstrated narrowing at the apex of the duodenal bulb and consider-

NOCTURNAL GASTRIC SECRETION/HCL MG/AND COURSE OF PEPTIC ULCER  
A.J.-255358-MALE-AGE 43-DUODENAL ULCER 1 YEAR DURATION

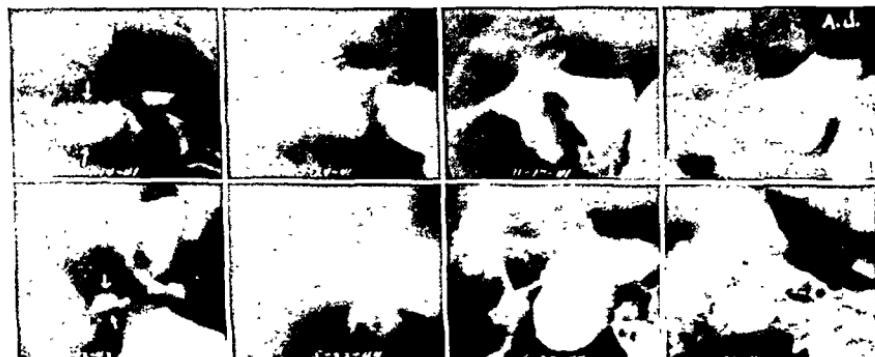
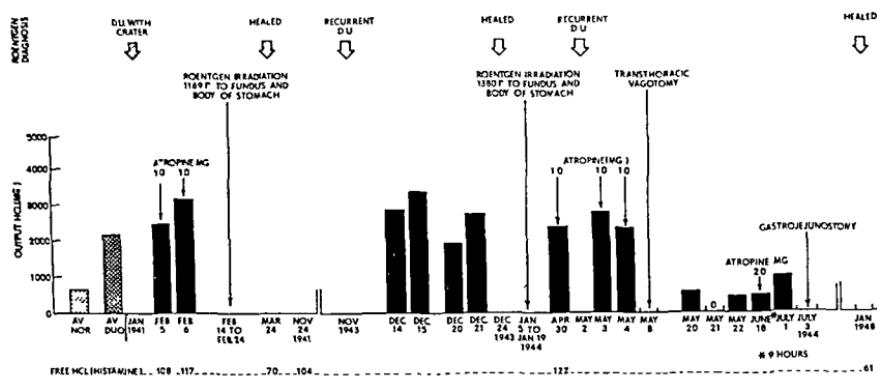


FIG. 3

able gastric retention. Gastric aspiration (6 p.m.-3 a.m.), 2.0 mg. of atropine being given at 7 p.m., yielded 466 mg. of acid and on July 1, 1028 mg. Operation, on July 3, 1944, disclosed a normal appearing stomach, and an ulcer scar on the posterior wall of the duodenal bulb; a gastrojejunostomy was performed. The patient has remained well during the subsequent three and one half years. The maximum acidity (histamine) in January 1948 was 61 units. X-ray examination revealed a well-functioning gastroenterostomy, with no evidence of stomal ulcer and only slight deformity at the apex of the duodenal bulb. Nocturnal gastric aspiration was attempted on February

21 and 22, 1948. Volumes of 834 and 741 cc. with average free acidities of 23 and 18 were obtained (output HCl, 518 and 492 mg.); however, the free acid in single hourly specimens rose to 66 and 48 units respectively. Since the almost continual reflux of intestinal content through the gastroenterostomy did not permit accurate measurements, these data are not recorded. The insulin test was positive, but nevertheless, vagotomy seems to have produced a marked reduction in the secretion of acid gastric juice. The patient has gained 54 pounds in weight since the vagotomy.

#### COMMENT

The persistence of severe ulcer pain despite the administration of large amounts of morphine and its subsidence following gastric aspiration clearly indicate the role of acid gastric juice in the mechanism of ulcer pain. The output of hydrochloric acid in the twelve hour nocturnal secretion, usually approximating 2940 mg., exceeded the average for patients with duodenal ulcer. The persistence of the hypersecretion despite the use of atropine conforms with the results obtained in other patients studied similarly. The continued hypersecretion following irradiation of the gastric fundus also is of interest, since a marked decrease in the nocturnal secretion has been observed in patients with active uncomplicated ulcer, receiving a depth dose of 1350 to 1710 r<sup>12</sup>. Gastric secretion decreased markedly after transthoracic vagotomy and, although the insulin test is positive, the course to date, three and one half years later, has been excellent.

*Case 4.* E. M. (Unit No. 370734) (Table 4, Fig. 4), a 61 year old male salesman, had experienced ulcer distress since July 1944. A perforated duodenal ulcer in July 1945 had been treated by simple closure. He first appeared at the University Clinics on November 26, 1945, having had recurrent pain for four months. Roentgen examination demonstrated an ulcer crater in a deformed duodenal bulb. The maximum free acidity (histamine) was 128 clinical units. The symptoms were relieved by an antacid regimen; complete healing of the crater was observed roentgenologically on February 22, 1946. Vomiting occurred several weeks later, however, and the patient was readmitted to the hospital on March 9, 1946. The symptoms subsided completely after five days of antacid therapy.

Readmission was necessary on July 6, 1946 because of vomiting of ten days' duration. The patient was markedly dehydrated and required large quantities of fluids parenterally. X-ray examination demonstrated a markedly deformed duodenal bulb with a centrally located crater. The nocturnal gastric secretion contained 3211 to 4921 mg. of hydrochloric acid. A transabdominal vagotomy and posterior gastroenterostomy were performed on July 16, 1946, with uneventful recovery. The insulin test postoperatively was interpreted as demonstrating "80 per cent decrease in vagus activity."

In January 1947 the patient noted a bloating sensation, nausea and vomiting, and a dull pain in the perumbilical region. Roentgen examination on February 11, 1947 indicated a probable ulcer crater in the jejunum. The nausea and vomiting increased, and the patient reentered the hospital on April 3, 1947. A large ulcer crater,

approximately 1.5 cm. in diameter, now was demonstrated in the efferent loop of the gastroenterostomy, 2 cm. below the site of anastomosis. The insulin test was positive. At operation, on April 11, the ulcer was easily found. A large vagus fiber located deep in the muscle on the posterior wall of the esophagus was excised. Segments of nerves were removed from the lesser curvature of the stomach, 1 cm. below the margin of the esophagus, and from smaller anterior and posterior fibers; the presence of nerve fascicles was confirmed histologically. Insulin tests three and fourteen days later were positive.

TABLE 4

*Twelve Hour Nocturnal Gastric Secretion and Clinical Course in Case 4 (E. M.)*

DATE	VOLUME	FREE	TOTAL	COMMENT
		HCl Cl. units	OUTPUT HCl mg.	
July, 1945				Suture Perforated Duodenal Ulcer
July 7, 1946	940	112	3828	
July 8	1396	97	4921	
July 9	1262	70	3211	
July 14				Duodenal Ulcer—Transabdominal Vagotomy, Posterior Gastroenterostomy
April 11, 1947				Jejunal ulcer—Second transabdominal Vagotomy
April 22-May 4				Irradiation Gastric Fundus and Body—1650 r (depth dose)
July 14, 1947				Jejunal ulcer—perforated at operation. Resection anastomosed jejunal segment—normal bowel continuity re-established
Aug. 14, 1947	1325	100	4892	
Aug. 15	1482	92	5151	Atropine 1 mg.
Aug. 18	1149	92	3818	Atropine 3.0 mg.
Aug. 20	1267	91	4331	Atropine 6.0 mg.
Aug. 27	1318	77	3649	Pituitrin 0.5 cc.
Aug. 30	1176	92	3933	
Sept. 7	1108	75	3044	
Oct. 10-15				Mild hematemesis, toxic reaction, and death

The maximum free acidity (histamine) on the eleventh post-operative day was 66 clinical units. Wangensteen aspiration postoperatively yielded 500 to 1400 cc. of gastric content daily. From April 22 to May 4, 1947, 1650 r (total depth dose) were directed to the fundus and body of the stomach. The stomal ulcer was again noted roentgenologically on May 7. A large subdiaphragmatic abscess developed along the greater curvature of the stomach, requiring drainage. The patient returned home on June 12, 1947, but was readmitted four weeks later because of vomiting and constant sharp burning pain below the umbilicus. He had lost 40 pounds in weight since the onset of ulcer symptoms.

Operation on July 14, 1947 disclosed numerous adhesions in the upper abdomen. A partial gastric resection was contemplated, but during the process of separating the transverse colon from the stomach in the region of the gastroenterostomy, a large jejunal ulcer perforated spontaneously. A four inch segment of jejunum containing

the perforation was resected and an end-to-end jejunostomy performed; the normal continuity of the bowel was re-established. The specimen contained an oval, penetrating ulcer, 2 cm. in its longest diameter. A severe alkalosis developed postopera-

NOCTURNAL GASTRIC SECRETION (HCL ING) AND COURSE OF PEPTIC ULCER  
E.M.-370734, MALE, AGE 41, DUE TO ULCER, 17 MONTHS DURATION  
PERFORATION 5 MO EARLIER

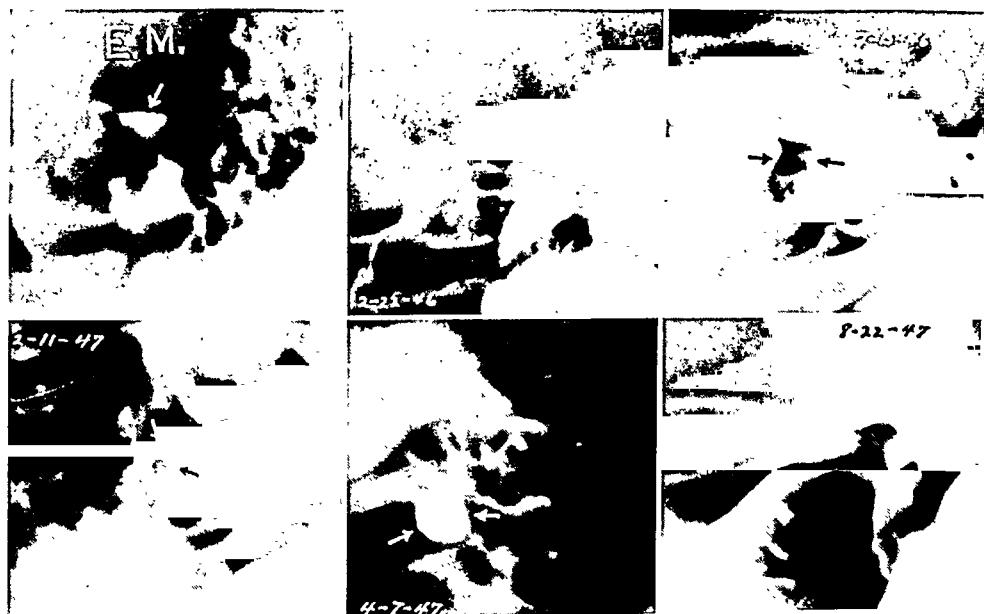
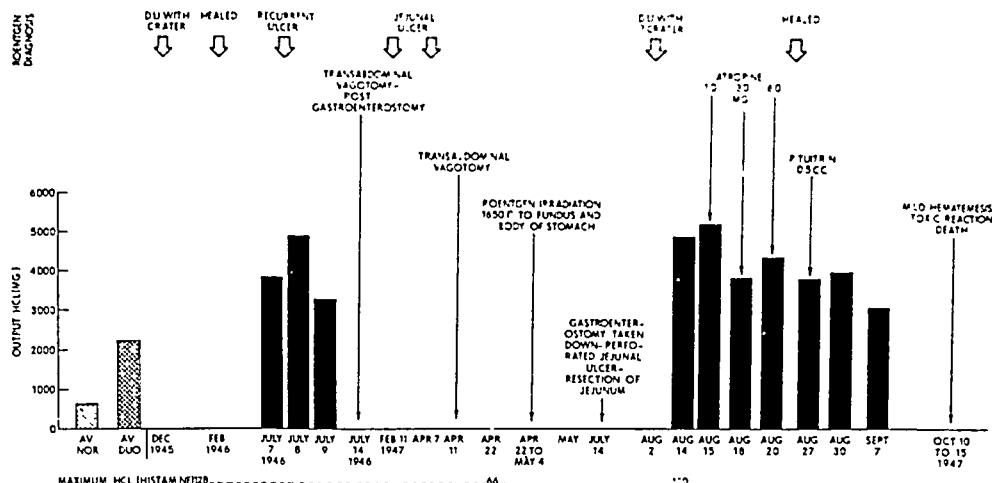


FIG. 4

tively, following the aspiration of large amounts of gastric content; the serum chloride decreased to 68 mM/L (normal 95–105), the CO<sub>2</sub> rose to 54.1 mM/L (normal 20–30) and the pH to 7.67. The electrolyte disturbance was corrected by the intravenous administration of isotonic saline solution. One month after this operation, the free

acid (histamine) rose to 120 units. Roentgen examination on August 2, 1947 revealed a questionable ulcer crater in the duodenal bulb; the width of the lumen was estimated as 5 mm. Three weeks later the lumen measured at least 8 mm. Twelve hour aspirations during the night yielded enormous quantities of hydrochloric acid not significantly affected by atropine in doses of 1, 3, and 6 mg., or by 0.5 cc. of pituitrin. Antacid therapy was reinstated and the patient left the hospital on September 9, 1947.

The final admission occurred on October 11, 1947, after several mild hematemeses. The blood pressure was 158 systolic and 100 diastolic. Approximately 300 cc. of blood were vomited on the following day. The erythrocytes measured 3.8 million per cubic mm. and the hemoglobin 12 grams. The patient became confused and irrational. The patient's condition progressively deteriorated and he died on October 15, 1947.

At autopsy both vagus nerves were located approximately 15 cm. above the esophago-gastric junction and were traced to within 3 or 4 cm. above the junction of the esophagus with the stomach. At this level branches passed through the esophageal hiatus and into the stomach. Several ligatures were found around branches of both vagus nerves at the esophago-gastric junction. Apparently viable nerve tissue was noted histologically in the walls of the esophagus and stomach. Numerous small hemorrhages were present in the gastric mucosa. The duodenum contained a healed ulcer. A fibrosed indurated area encircling the wall of the jejunum represented the site of the old gastrojejunostomy. The remainder of the gastrointestinal tract appeared normal, except for marked hyperemia of the rectal mucosa. The center of the liver contained a large, encapsulated, well-differentiated hepatoma, measuring approximately 14 x 6 cms. The brain appeared normal grossly except for mild edema; the histologic findings were interpreted as those of a mild diffuse cortical toxic encephalopathy. Additional diagnoses included generalized arteriosclerosis, cardiac hypertrophy, old occlusion of the right coronary artery, bilateral confluent bronchopneumonia with early abscess formation, and acute and chronic peptic esophagitis.

#### COMMENT

The course in this patient was characterized, during a three year period, by the perforation of a duodenal ulcer and by recurrent jejunal ulcers after each of two vagotomies. The nocturnal output of hydrochloric acid ranged from 3044 to 5151 mg., averaging 3987, much greater than the mean for duodenal ulcer. It was not consistently lowered by two vagotomies, albeit incomplete. Roentgen irradiation, and atropine, in doses up to 6.0 mg. in twelve hours, likewise had no demonstrable inhibitory effect. The presence of intact vagus fibers at autopsy despite two vagotomies is of particular interest.

*Case 5.* G. S. (Unit No. 404603) (Table 5, Fig. 5), a 46 year old male clerk, had experienced recurrent ulcer distress for 20 years. A partial gastrectomy had been performed elsewhere on February 20, 1947, with resection of an estimated three fourths of the stomach and removal of the mucosa from the first portion of the duo-

denum. Ulcer distress reappeared two and one half weeks after operation; the patient entered the Billings Hospital on March 29, 1947. The maximum free acidity (histamine) was 128 clinical units. Roentgen study revealed a huge penetrating jejunal ulcer in the efferent loop of the gastroenterostomy, located slightly below the site of anastomosis. The introduction of 200 cc. of 0.5 per cent solution of hydrochloric acid into the stomach evoked severe pain, nausea and vomiting within 10 minutes. Treatment initially consisted of a standard antacid regimen, including calcium carbonate at hourly intervals, 1 mg. of atropine in the evening, and sedatives. The pain was relieved by nightly (9:30 p.m.) aspirations of 30 to 450 cc.

TABLE 5

*Twelve Hour Nocturnal Gastric Secretion and Clinical Course in Case 5 (G. S.)*

DATE	VOLUME cc.	FREE HCl Cl. units	TOTAL OUTPUT HCl mg.	COMMENT	
Feb. 20, 1947					Duodenal Ulcer—Partial gastrectomy and removal duodenal mucosa
March 11					Jejunal Ulcer
April 2	1600	95	5533		
April 8	1830	88	5846		
April 9	2050	69	5142		
April 11					Transthoracic Vagotomy
April 15	478	5	84		
May 2	400	40	582		
May 6	845	40	1230		
Sept. 29					Jejunal Ulcer
Oct. 2	1315	94	4555		
Oct. 4	1015	63	2496	10 hours	
Oct. 5	1180	55	2367	Enterogastrone 2000 mg.	
Oct. 6	910	51	1693	7 hours	
Oct. 22					Transabdominal Vagotomy—Repair gastrojejunocolic fistula
Oct. 27					Persistent jejunal ulcer—massive hemorrhage—death

of gastric content, containing up to 120 clinical units of free acid. Twelve hour aspirations yielded from 5142 to 5846 mg. of hydrochloric acid, averaging 5507 mg. A severe alkalosis developed, with a serum  $\text{CO}_2$  of 52 mM/L and serum chloride of 80.8 mM/L; the acid-base disturbance was corrected promptly by the parenteral and oral administration of ammonium and sodium chloride.

A transthoracic vagotomy was performed on April 11, 1947. Three large vagal trunks, two anterior and one posterior, and numerous small communicating fibers were identified over a 4 inch segment and excised. Ten "acid tests" were performed, beginning on the second postoperative day. The pain response gradually decreased and after the eleventh postoperative day, it could no longer be elicited. The insulin test on the twelfth day was negative. The maximum acidity on the twenty-third day was 52 units. The nocturnal gastric secretion diminished markedly (Table 5). Roentgen examination demonstrated partial healing of the ulcer crater on April 24 and complete healing on May 9. The patient left the hospital on May 10, 1947.

X-Rays on July 2, 1947 indicated a well-functioning gastroenterostomy. The maximum free acidity on August 5 was 95 clinical units.

The patient reentered the hospital on September 29, 1947, because of progressively increasing pain in the epigastric and periumbilical regions. Roentgen and gastroscopic examinations disclosed a recurrent jejunal ulcer. Two insulin tests yielded inconclusive results. The twelve hour nocturnal gastric secretion contained 4555 mg. of hydrochloric acid. The following evening (Oct. 3) the patient suddenly ex-

NOCTURNAL GASTRIC SECRETION(HCL MG.) AND COURSE OF PEPTIC ULCER.  
GS-404603-MALE-AGE 46-DUODENAL ULCER, 20 YEARS DURATION

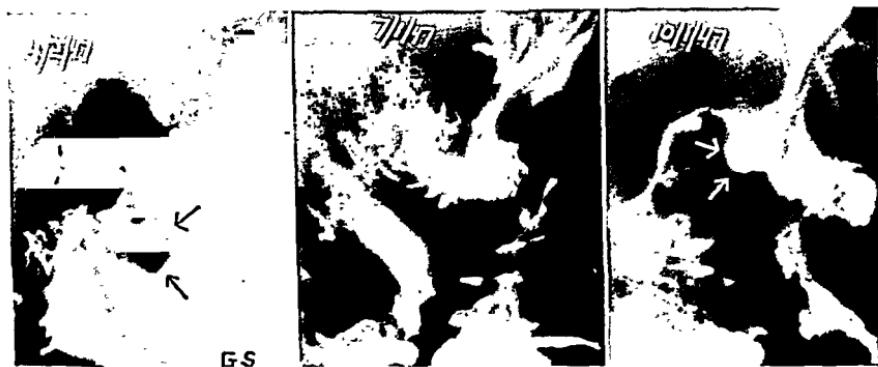
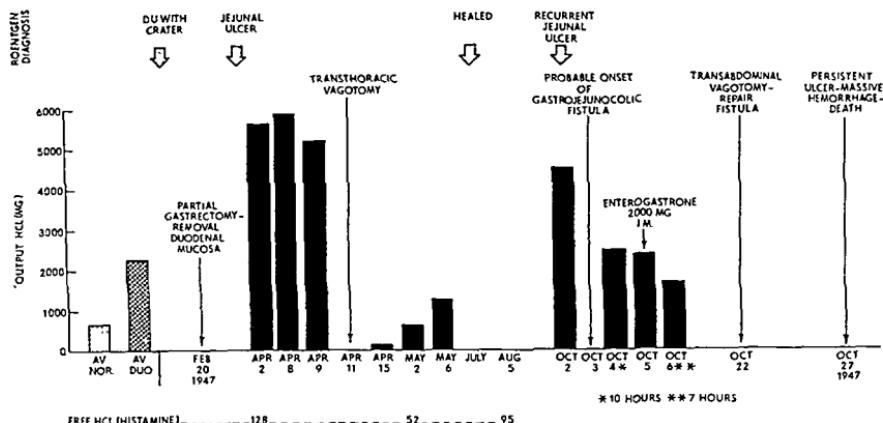


FIG. 5

perienced a severe pain across the lower chest and upper abdomen, with rigidity of the abdominal wall, suggesting perforation of the ulcer. The pain and rigidity subsided with continued gastric aspiration. However, brownish material appeared intermittently in the gastric contents thereafter. Three satisfactory measurements of the nocturnal secretion were obtained subsequently, the output of acid exceeding the average values for patients with duodenal ulcer during similar periods of the night. The free acidity of clear aspirates ranged from 94 to 115 clinical units.

A third operation was performed on October 22, 1947. The efferent loop of jejunum was adherent to the left transverse colon at a point two inches beyond the gastro-

jejunostomy. A fistulous tract between the colon and the jejunum, large enough to admit the index finger, was located at this site. The jejunum, approximately one foot beyond this area, was firmly adherent to the posterior abdominal wall by a short fibrous band, apparently causing obstruction. A separate intact vagus fiber passing from the site of previous ligation of the posterior vagus nerve was excised. A structure, presumably the distal end of the anterior vagus from its point of previous ligation and division, was located at the level of the cardia and severed. The presence of nerve fascicles later was confirmed histologically. The fistulous connection was resected and the defects in the colon and jejunum were repaired. On the fourth post-operative day (October 26) the patient vomited a small amount of blood; he was given 1500 cc. of plasma. Massive hemorrhage occurred on the following day; the blood pressure decreased to 90 mm. of mercury systolic and 60 diastolic. The erythrocyte count diminished to 1.09 million and the hemoglobin to 3.3 grams. Temporary improvement followed the administration of 1800 cc. of whole blood and 1200 cc. of plasma. The bleeding recurred, however, and, despite an additional 2300 cc. of whole blood and 500 cc. of plasma, the blood pressure fell to 70 mm. mercury systolic and 40 mm. diastolic; the patient succumbed shortly thereafter.

Autopsy revealed massive hemorrhage into the gastrointestinal tract, arising in a large jejunal ulcer 8 x 5 cm. in diameter, located at the posterior margin of the gastro-jejunostomy. The center of the ulcer contained an eroded thickened artery. The vagus nerves were traced from the midportion of the esophagus to the stomach; at no point were any of the larger fibers continuous with those on the gastric wall. Histologically, however, a number of apparently viable nerve trunks were identified between the muscle layers of the esophagus and stomach.

The pancreas contained an islet cell carcinoma; one metastasis was found in the liver. It is of interest that the fasting blood sugar had ranged from 50 to 84 mg. per cent (normal 60-90). There had been no symptoms of hypoglycemia, except during the insulin tests; the response to this procedure had not differed from that of other individuals, and the patient had undergone several periods of fasting without untoward clinical manifestations. Both adrenal glands were enlarged and contained numerous cortical adenomas. Additional findings included mucous plugs in the main bronchi with atelectasis of both lower lobes, pulmonary edema, and sclerosis of the coronary arteries.

#### COMMENT

This patient manifested a truly intractable tendency to ulcer formation. The marked hypersecretion and development of a jejunal ulcer several weeks after partial gastrectomy and removal of the mucosa from the duodenal bulb is of particular importance in view of the renewed interest in resection of the antrum for the treatment of peptic ulcer<sup>13</sup>. Friedell, Shaar and Walters<sup>14</sup> have demonstrated the correlation between continued high acid levels and persistent or recurrent ulcer following gastric surgery. In this case, a jejunal ulcer complicated by gastrojejunocolic fistula developed after transthoracic vagotomy and progressed to fatal hemorrhage in spite of a further transabdominal vagotomy. The output of hydrochloric acid before vagotomy approximated an average of 5507 mg., more than twice the mean for patients

with uncomplicated duodenal ulcer. This was markedly reduced temporarily by transthoracic vagotomy, even though the procedure was later shown to have been incomplete. The ulcer healed, but recurred later when the secretory level also was found to have returned.

#### GENERAL COMMENT

The nocturnal gastric secretion was excessive in all five cases, exceeding not only the mean for normal persons by four to seven times, but surpassing also the general average for patients with duodenal ulcer. The output of hydrochloric acid was not reduced by "medical vagotomy", for atropine in therapeutic doses up to 6.0 mg., under the conditions of the study, had no consistently significant effect in the four cases so treated. This finding is in contrast to previous reports of a reduction in the volume of secretion following the use of atropine. Grossman and Ivy<sup>15</sup> have indicated that knowledge concerning the influence of atropine upon human gastric secretion is incomplete. The present results suggest, possibly, that mechanisms other than, or in addition to, "secretory hypertonus of the vagus nerves", operate to maintain an excessive production of hydrochloric acid. Larger amounts of atropine might have been more effective, but might also have produced toxic effects.

The intramuscular administration of 2000 to 5000 mg. of an enterogastrone concentrate also failed to reduce the nocturnal gastric secretion in the three patients studied. Irradiation of the fundus and body of the stomach, though effectively diminishing the output of acid in many patients with peptic ulcer<sup>16</sup>, yielded erratic results. Thus, gastric secretion remained lowered in only one patient; a temporary decrease occurred in one; there was no reduction in two. Section of the vagus nerves was followed in two instances by a pronounced decrease in the output of acid and by healing of the ulcer. In each of two patients the vagotomy was incomplete, gastric secretion was not permanently reduced, and ulcers recurred subsequently. In one of these, a marked hypersecretion had been present despite resection of three-fourths of the stomach, including the antrum.

The clinical course of these five patients was characterized by severe pain and by serious complications; these included massive hemorrhage, perforation, recurrent ulcers after partial gastrectomy and after vagotomy, and gastrojejunocolic fistula. Large doses of morphine and analgesics were completely ineffective in controlling ulcer pain in Cases 1 and 2; it subsided only after the administration of large amounts of alkali and repeated gastric aspirations. Two patients died; in one the cause was not determined precisely, although it apparently was not directly attributable to peptic ulcer; in the other death resulted from massive bleeding arising in a persistent jejunal ulcer. It is of interest that a well-differentiated hepatoma was present in one of these cases and an islet-cell carcinoma of the pancreas in the other.

The prompt healing of peptic ulcer in three patients following reduction in

subjects secrete a high volume of gastric juice during the night, with relatively high hydrochloric acid concentration. Five of our twenty-three normal healthy control subjects had a nocturnal total free acid output nearly two to two-and-one-half times that of the average of our ulcer patients.

While I agree that one can demonstrate high nocturnal secretion in some ulcer patients as the authors have so ably described, I believe that there are also other factors involved in intractability; namely, penetration, walled-off pin-point perforation, low grade pancreatitis, a tensional state not necessarily associated with hypersecretion, and so forth and so on. The question of tissue resistance might also be taken into consideration. I am certain that Dr. Kirsner does not concentrate on acid studies to the exclusion of other causes for intractability.

With reference to the general statements usually made, to the effect that patients with duodenal ulcer have, as a rule, an excessive nocturnal gastric secretion as compared with normal healthy subjects, I should like to point out that the few studies that have been done to date yield some conflicting data which as yet have not been adequately explained.

It is possible that the conflicting data might be explained by the variation in the experimental methods employed by the different workers in the field. It therefore appears to me that additional nocturnal studies by a coordinated method are necessary on both normal subjects and ulcer patients, both during the active and quiescent state of the ulcer, during periods with and without antacid therapy, and in patients with and without ulcer complications. It is an intriguing aspect of the ulcer problem and certainly warrants further efforts such as have been presented to us here by the authors.

**DR. ASHER WINKELSTEIN (New York, N. Y.):** Dr. Bockus and Fellow Members:

We are pleased when a paper on night secretion appears from Dr. Walter Palmer's clinic, because his clinic confirms our own studies during the past twenty years on this subject.

We have made three such studies on the night secretion, one alone, and two with Drs. F. Hollander and A. Cornell. They established the fact that both the acidity and volume are increased during the night in duodenal ulcer patients. This has been amply confirmed by Henning, Valdez, Dragstedt, and Levin. The only dissenting voice is that of Dr. David Sandweiss.

Dr. Sandweiss used very heavy meals before the night study; very mild ambulatory ulcer patients; nervous medical students as controls; and upset the duodenal regulatory mechanism by continuous suction. We, therefore, do not agree with his contention that normals and ulcer patients have the same volume and concentration of acid during the night.

With reference to the practical implications of the cases that were presented here this morning, we have found no method of controlling the night secretion with any form of medical therapy, other than the continuous intragastric drip therapy during the night. We have gotten very good pH's—3.5 to 4. Also we have been able to control many refractory cases even such as have been shown here this morning. I venture to suggest that had Drs. Kirsner and Levin tried the use of the continuous

night intragastric drop therapy in this group of patients, they would have been able to control their symptoms.

Surgically, we have found that vagotomy alone does not control the night secretion to the point of achlorhydria. It merely reduces the volume. Gastroenterostomy, when combined with vagotomy, has given us a 50 per cent incidence of achlorhydria. We have found a striking fact, and that is, if you combine total subtotal gastrectomy with vagotomy, you get an achlorhydria in 94 per cent of the cases.

Gastronenterologists and surgeons are familiar with a small group of cases who are so-called "surgically incurable duodenal ulcers" and resemble malignancies in their tendency to recur and recur. It is exactly in that group that complete vagotomy plus subtotal gastrectomy followed by achlorhydria will usually give you a complete cure.

We advocate the use of the intragastric night drip for intractable ulcers with high night secretion. We think that that is the most important disturbance of the stomach in peptic ulcer. We also advocate subtotal gastrectomy plus bilateral vagotomy in the surgical therapy of duodenal ulcer.

DR. JOSEPH B. KIRSNER (Chicago, Ill.): I should like to thank Dr. Sandweiss and Dr. Winkelstein for their remarks. I think we are all agreed that there probably are several factors involved in the pathogenesis of peptic ulcer, including tissue resistance. In this particular group of patients, however, hypersecretion obviously played a predominant role. Concerning the presence of a high acid secretion in apparently normal individuals, you may recall that in the studies reported by Dr. Levin last year only four per cent of normal subjects produced more than a thousand mg. of acid in the 12-hour nocturnal secretion, whereas more than 80 per cent of the duodenal ulcer group secreted acid in excess of 1000 mg. I should like to take this opportunity to point out that while we have considered antacid therapy, roentgen irradiation, and vagotomy in the treatment of peptic ulcer, under Dr. Palmer's guidance, we emphasize the total management of the ulcer patient.

I am in complete accord with the suggestion of Dr. Sandweiss that additional studies on night secretion by other investigators, utilizing a coordinated method of approach would yield additional valuable data.

It is gratifying to learn that our observations coincide with Dr. Winkelstein's views. We have not employed the intragastric drip primarily because the majority of our patients have responded to usual therapeutic measures. However, the continuous intragastric drip, by eliminating the cephalic phase of gastric secretion certainly exerts an inhibitory influence upon the output of acid.

We have not felt inclined to recommend subtotal gastrectomy and vagotomy in the surgical treatment of duodenal ulcer. This topic is to be considered in more detail later today. As to the question of why partial gastrectomy was not performed in these patients, it was carried out in one case and a jejunal ulcer developed several weeks later. It was contemplated in a second patient, but the perforation of a jejunal ulcer necessitated the simpler procedure. The remaining three patients responded eventually to more conservative methods of treatment.

Thank you!

## BENIGN STRICTURE OF THE ESOPHAGUS\*

### WITH SPECIAL REFERENCE TO ESOPHAGITIS, HIATUS HERNIA, ESOPHAGEAL ULCER, AND DUODENAL ULCER

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#### INTRODUCTION

Our interest in benign stricture of the esophagus occurring in association with esophagitis was aroused by a case (reported by Benedict and Daland<sup>1</sup>) in which benign stricture occurred a few weeks after gastric resection for duodenal ulcer and the use of an inlying intranasal Levine tube. Jackson<sup>2</sup> had previously reported 3 cases of esophageal stenosis associated with ulcer of the stomach and duodenum. Vinson and Butt<sup>3</sup> have stated that esophagitis is the commonest disease of the esophagus, and Olsen<sup>4</sup> in a recent editorial remarked that esophagitis is a subject which has not received the attention it deserves in medical literature. In 1946 one of us (EBB)<sup>5</sup> commented on 44 cases of benign stricture of the esophagus. All of these cases had esophagitis, and some of them had other lesions associated, namely hiatus hernia, duodenal ulcer, esophageal ulcer.

Esophagitis in many cases seems to be directly related to other diseases of the gastrointestinal tract, especially to those in which vomiting or regurgitation of acid gastric secretions is of frequent occurrence. In a pathological and clinical study of 82 cases of acute ulcerative esophagitis, Bartels<sup>6</sup> found gastric contents in the esophagus in all cases at necropsy. It is interesting to note that Selye<sup>7</sup> produced hemorrhagic esophagitis by ligating the pylorus in experimental animals. Olsen and Harrington<sup>8</sup> have shown that an actual shortening of the esophagus may occur at the esophagogastric junction. They believe repeated episodes of ulcerative esophagitis and healing of the esophagus are usually responsible for the short esophagus type of esophageal hiatal hernia.

Benign stricture of the esophagus is a general term which means narrowing of the esophagus. Although it is a rare disease, it is encountered quite frequently by the endoscopist and the thoracic surgeon. In this paper we shall discuss 60 cases in all of which the stricture was associated with esophagitis, and in some of which there was also hiatus hernia, duodenal ulcer or esophageal ulcer. There were 18 with esophagitis alone, 34 with hiatus hernia, 20 with duodenal ulcer, and 16 with esophageal ulcer. Six patients had all three, namely hiatus hernia, duodenal ulcer, and esophageal ulcer. Strangely enough, there were

\* Presented at the Annual Meeting of The American Gastroenterological Association, Atlantic City, May 1, 1948.

none with gastric ulcer. Six were heavy users of alcohol and six used alcohol moderately. Seven patients gave a history of gallbladder attacks within a few months to a year of the time of the stricture. Two patients had ulcerative colitis, and one had an exacerbation of esophagitis and stricture following streptococcus sore throat. There were 42 males, and 18 females. Two patients were only 15 years old, one was 25, 17 were between 30 and 50, and 35 (or 58%) were between 50 and 70. Four patients were between 70 and 80, and one was 82.

#### SYMPTOMATOLOGY

The outstanding symptom of benign stricture of the esophagus is dysphagia, varying from slight difficulty with solid foods to complete inability to swallow any liquids at all. Regurgitation is common, usually without nausea and without real vomiting. If ulceration is present, hematemesis may occur. Heartburn is frequent, with distress and substernal or subxiphoid pain if there is ulceration. Anorexia is also common. Inability to belch is frequently noted.

#### DIAGNOSIS

The diagnosis is made by history, x-ray examination, and esophagoscopy. Physical examination usually contributes nothing. By history alone, it is impossible to differentiate benign stricture from carcinoma, the most important differentiation of all. X-ray examination, although very helpful and essential, also fails on numerous occasions to differentiate benign stricture from carcinoma (Fig. 1). By esophagoscopy, a smooth conical narrowing usually means a benign stricture but occasionally the endoscopist may be confused with a smooth constricting annular carcinoma. Even biopsy may be in error since it may show only the inflammatory process associated with a carcinoma and may not have been taken deeply enough to get the truly malignant nature of the disease. In doubtful cases esophagoscopy and biopsy should be repeated. In order to avoid a false negative report, biopsy must be obtained from deep within the lumen of the stricture.

#### TREATMENT

The treatment of benign stricture of the esophagus is bouginage or surgery.

*Bouginage.* Since every case of benign stricture requires at least one esophagoscopy with biopsy for diagnostic purposes, bouginage should be carried out at the time of the first esophagoscopy. If the biopsy is unsatisfactory and there is still a question of carcinoma, esophagoscopy should be repeated, at which time further bouginage and biopsy can be performed. If dysphagia continues the patient is asked to swallow a thread which is used as a guide to

further bouginage. This may be done either in the office or in the Out Patient Department. A bland diet of liquids and strained foods as tolerated is important. Frequent feedings are indicated. Antacids may be useful. Alcohol and tobacco are interdicted.



FIG. 1. S. B. U#602736. MALE 72 CARCINOMA OF ESOPHAGUS

First x-ray doubtful whether malignant or benign. First esophagoscopy and biopsy—benign stricture, chronic inflammation. Second esophagoscopy and biopsy—squamous cell carcinoma, grade II.

In this series, 43 cases were treated by bouginage. There were 23 good results (Figs. 2-5 incl.) (able to eat solid food normally), 11 fair results (living mostly on finely ground or strained foods), 4 poor results (living mostly on liquids) and 5 not followed. The 4 poor results were as follows:

(1) A man 82 years of age with an esophageal ulcer required esophagoscopy and bouginage on 4 occasions over a period of 3 years. This patient did very well for 3 years after the first esophagoscopy in 1940, but then required 3

esophagoscopies in 1943. He was too old to consider for surgery. He died of pneumonia in 1944.

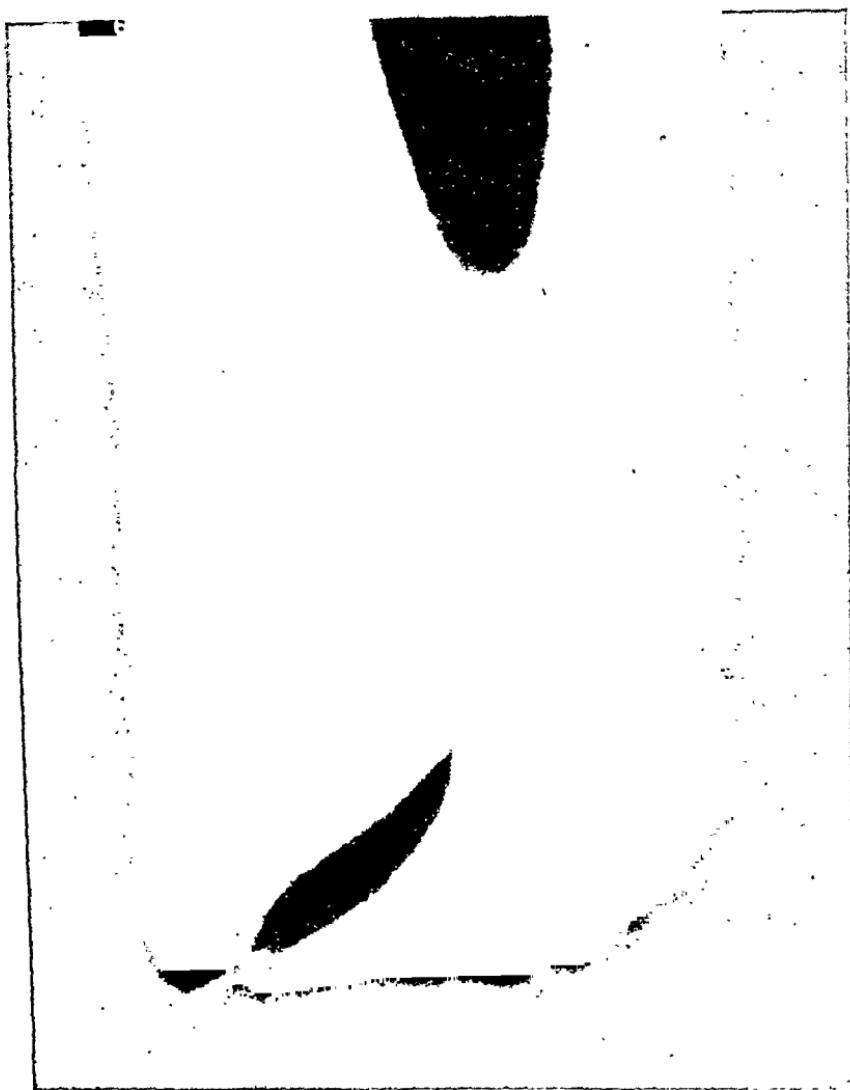


FIG. 2. H. M. U #360065 FEMALE 50 BENIGN STRICTURE  
Esophagitis. No hiatus hernia, esophageal ulcer or duodenal ulcer. Dysphagia 7 months.  
Tolerating liquids only for 3 months. Loss of 60 lbs. in 7 months. First x-ray erroneously reported  
probable annular carcinoma.

(2) A man 56 years of age who had both hiatus hernia and esophageal ulcer. This patient was uncooperative and came for treatment only once or twice a year when en route from Maine to Florida. He permitted esophagoscopy only twice in 5 years, refused to swallow a thread and refused surgery.

(3) A man 52 years of age with esophagitis, a benign stricture 13 cm. long at first but later reduced to 7 cm. in length, coarctation of the aorta and morphine addiction, was able to get along on liquids and strained foods with

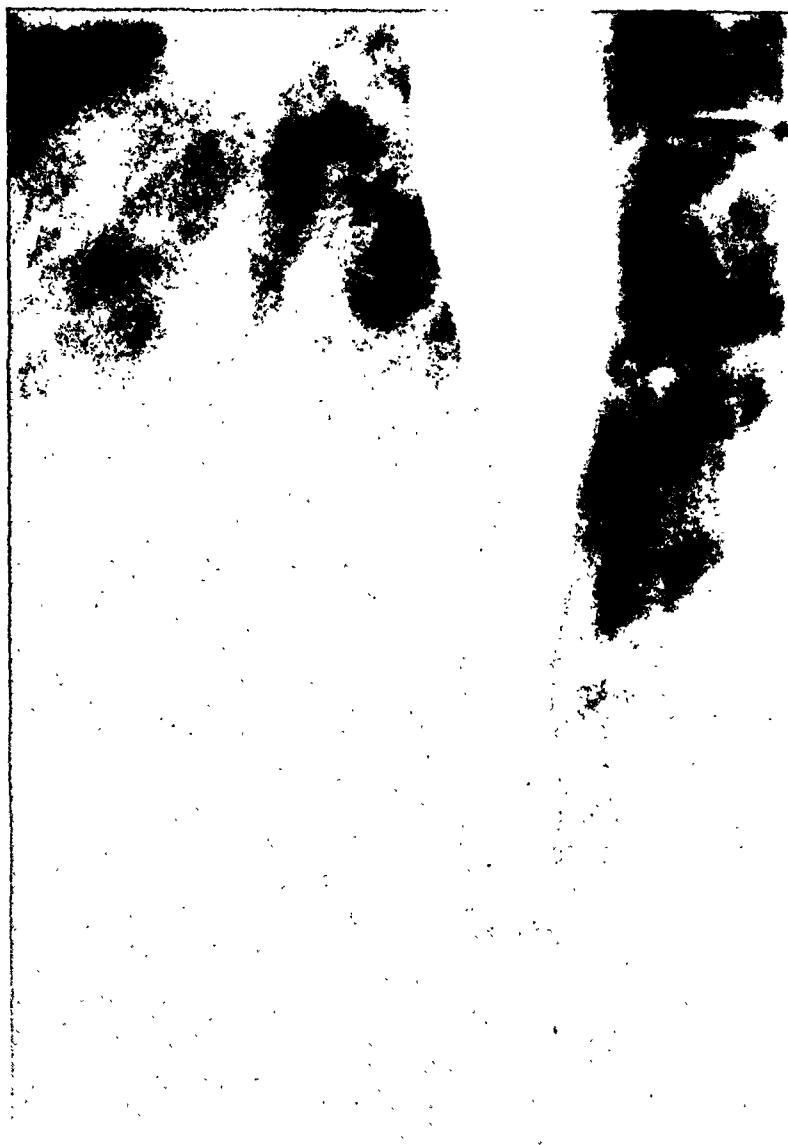


FIG. 3. H. M. U#360065

Same patient as shown in Fig. 2 after 3 esophagogoscopies and 6 bouginage treatments during a 6 months' period using a thread as a guide. Gain of 60 lbs. in 6 months.

esophagoscopy and bouginage about 4 times each year for a period of 5 years. He refused surgery and finally died of a perforated esophagus 2 days after the 22nd esophagoscopy and bouginage.

(4) A man 63 years of age with hiatus hernia and benign stricture who had

such marked language difficulty and was so uncooperative it was impossible to treat him satisfactorily.



FIG. 4. T. J. D. U# 523397 MALE 37 BENIGN STRicture  
Esophagitis. No hiatus hernia, esophageal ulcer or duodenal ulcer. Recent drinking bout of 3 months' duration, able to take liquids only, loss 30 lbs. in wgt. Preop. x-ray showing benign stricture.

**Surgery.** Broadly speaking there is only one indication for surgery and that is failure of bouginage. Failure of bouginage may be variously interpreted. The elderly poor surgical risk had better get along on strained foods than to undergo a major surgical procedure for a benign stricture. Recurring attacks of dysphagia with pain and hemorrhage from an esophageal ulcer, uncontrolled

by diet and bouginage are good indications for surgery in a good risk patient. The danger of malignancy, as an indication for surgery, has been overemphasized, since a good esophagoscopist can rule it out by adequate biopsy. One

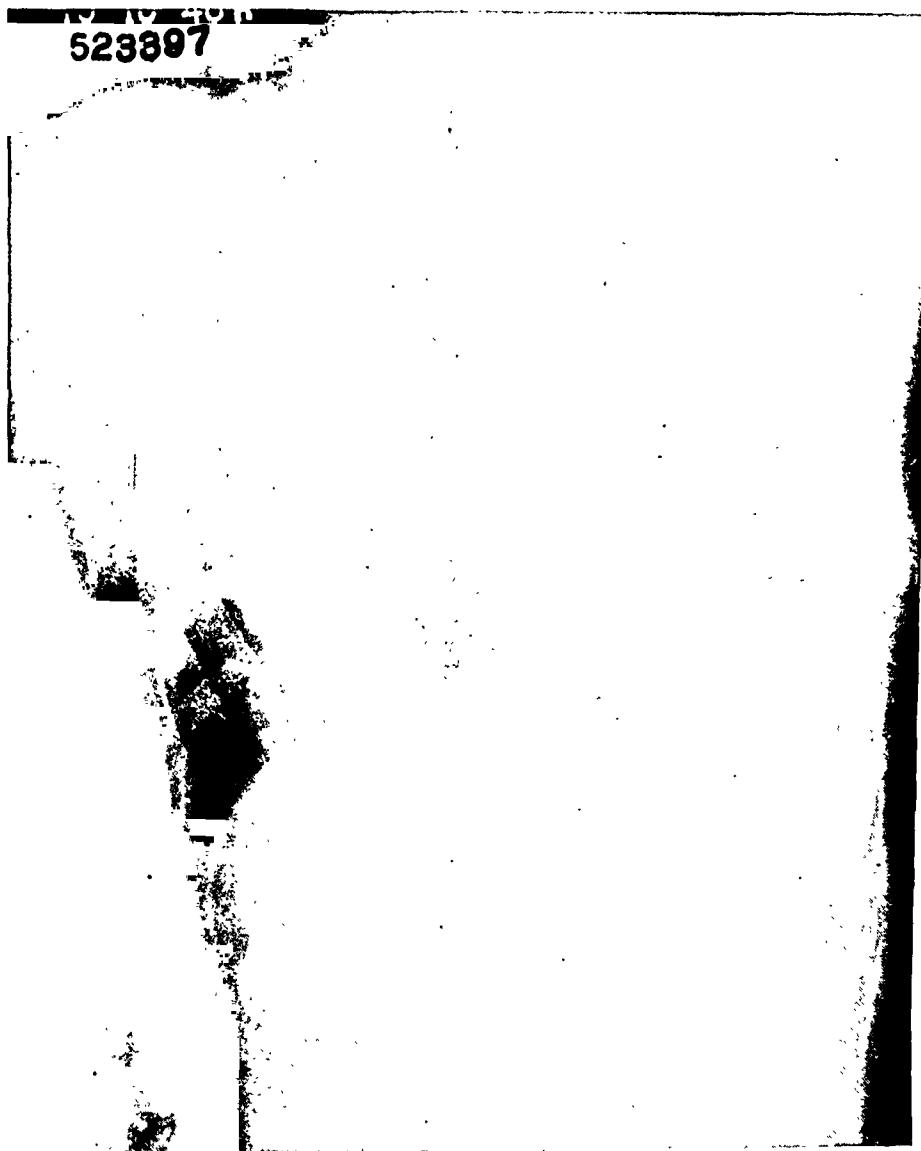


FIG. 5. T. J. D. U#423397

Same patient as shown in Fig. 4, 7 months later after 2 esophagoscopies and bouginage 8 times using thread as a guide. Narrowing persists by x-ray but patient is symptom-free and has gained 30 lbs.

of us (EBB)<sup>9</sup> has reported carcinoma developing in a lye stricture and in a congenital stricture. Since that report we have had one case of carcinoma (included in this series) developing in a benign stricture associated with hiatus hernia, duodenal ulcer, and esophageal ulcer after having been treated by

esophagoscopy and bouginage for 19 years in another city. On the first biopsy done here (EBB) the report was adenocarcinoma, resection (RHS) was carried out with very high anastomosis. In a second similar case, a small unexpected carcinoma was found while resecting the lower esophagus for inflammatory stricture. This patient had had an esophagoscopy at another hospital.

When it becomes apparent in any case of benign stricture that bouginage is inadequate, the choice of operation depends upon the length of esophagus which is involved. If the stricture is located in one small segment with only an annular stenosis and very little longitudinal extension, it may be possible to perform a local plastic procedure which will be sufficient to overcome the obstruction. This situation is found more frequently in the cardia than at any other level. The surgical maneuver consists merely in making a longitudinal incision from normal esophagus above to normal esophagus or stomach below. The incision is then closed circumferentially using carefully placed interrupted sutures of silk in three layers. This procedure eliminates the narrowed portion in the cases where it is applicable. Of the 17 patients in the present series who required surgical relief, 3 were treated by longitudinal incision and circumferential closure with excellent results.

In a larger percentage of the cases where surgical treatment is required, it is necessary to perform a resection of the lesion. The technic used in such cases is identical with that which is practiced in the case of carcinoma of the esophagus.<sup>10, 11</sup> The operation consists in excising the diseased area, closing the gastric end and performing an immediate esophagogastric anastomosis in the lower portion of the chest. Although one would think it unnecessary to divide the esophagus very far above the diseased area because of the nonmalignant nature of the lesion, it is wise to exceed the limits of the diseased area by several centimeters of normal esophagus. If the transection is made too close there may be a tendency for the esophagitis to recur in the supposedly normal proximal end. This complication occurred in one of the 14 patients on whom a resection was performed. The resulting stricture responded fairly well to treatment by bouginage. Another patient died postoperatively of a combination of the effects of coronary infarction and pulmonary embolism. The cause of death was proven by autopsy. The remaining 12 patients have been completely relieved of symptoms and have shown no further tendency to develop esophagitis.

#### ANALYSIS OF RESULTS

*Duodenal Ulcer.* The results in 14 duodenal ulcer cases with benign stricture but without esophageal ulcer and without regard to the presence or absence of hiatus hernia were as follows:

Twelve were treated by esophagoscopy and bouginage, 4 with good results, 4 with fair results, one with poor result (the morphine addict with the long

stricture who refused surgery), and 3 with no follow-up. Two patients in this group had resection of the lower end of the esophagus, one with a good result, and one died of pulmonary embolus.

*Esophageal Ulcer.* The results in 10 esophageal ulcer cases with benign stricture but without duodenal ulcer and without regard to the presence or absence of hiatus hernia were as follows:

Six patients were treated by esophagoscopy and bouginage, 4 with good results and 2 with poor results. (These 2 cases have been mentioned above; one was the man of 82; the other was one of the uncooperative patients.) Four had resections of the lower end of the esophagus with good results.

*Esophageal Ulcer and Duodenal Ulcer.* There were 6 patients in this group all of whom had, in addition, a hiatus hernia. The results were as follows:

Three were treated by esophagoscopy and bouginage, 2 of whom had good results and one fair result (short follow-up). Three were treated by resection of the lower end of the esophagus, 2 with good results, and one with a stricture at the esophagogastric anastomosis.

#### DISCUSSION

It had been hoped that analysis of 60 cases of benign stricture of the esophagus would enable us to state with some degree of assurance that certain groups should be treated by bouginage and certain other groups should be treated by resection. It is evident, however, that there are no hard and fast indications for surgery, because fairly good results have been obtained by esophagoscopy and bouginage in many patients who had duodenal ulcer or esophageal ulcer or both, with benign stricture. Furthermore, since most benign strictures occur in the older age groups, and since there has been one death and one postoperative stricture in 17 surgical cases, it is obvious that this is a major procedure not to be performed lightly for a benign condition.

#### CONCLUSIONS

Sixty cases of benign stricture of the esophagus have been reported. All of these were based on esophagitis. Many of these patients had hiatus hernia or duodenal ulcer or esophageal ulcer in various combinations. Six patients had all of these conditions together, namely benign stricture, esophagitis, hiatus hernia, esophageal ulcer, and duodenal ulcer.

Regurgitation of acid gastric secretions probably plays an important role in the etiology of esophagitis and benign stricture.

It is of very great importance to differentiate benign stricture of the esophagus from carcinoma by esophagoscopy and biopsy. In the face of persistent symptoms or doubtful x-ray examination, one negative biopsy is insufficient, and under those circumstances esophagoscopy and biopsy should be

repeated. The biopsy must be obtained from deep within the lumen of the stricture.

Bouginage combined with dietary treatment has given satisfactory results in over two-thirds of the cases. If adequate bouginage fails in a good risk patient, surgery is indicated. Because of the inflammatory nature of the disease and the length of the stricture, plastic repair is usually difficult. In most cases, herefore, the operation of choice is resection.

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#### DISCUSSION

DR. H. J. MOERSCH (Rochester, Minn.): Dr. Bockus, Ladies and Gentlemen: Dr. Benedict and Dr. Sweet have certainly demonstrated the important role that esophagitis, either alone or in association with other disturbances of the upper part of the gastro-intestinal tract, may play in the formation of esophageal stricture.

A year ago two of my associates, Dr. Olsen and Dr. Harrington, reviewed a large series of cases of short esophagus with intrathoracic stomach, and found that in 70 per cent esophagitis was associated, either alone or in company with some other disturbance of the upper part of the gastro-intestinal tract.

It is indeed surprising the rapidity with which shortening of the esophagus may occur secondary to esophagitis.

With Dr. Benedict's permission, I should like to show one slide which will illustrate this point.

(Slide) This patient was a woman who had had epigastric distress, regurgitation and belching for nearly two years. When she was examined at the clinic she was found to have a definite hiatus hernia. Esophagoscopy proved the hiatal hernia to be of the sliding type, with marked evidence of associated esophagitis. In spite of medical management, the patient's symptoms continued. Finally, she was operated on and the hiatal hernia was repaired. She remained symptom free for a period of a

year and a half. Then dysphagia again developed, the food lodging under the middle of the sternum. Roentgenologic examination of the esophagus revealed a stricture situated high in the esophagus. At esophagoscopy a stricture was found at the junction of the upper and middle parts of the esophagus. The mucosa below the stricture appeared to be normal, but study of a section removed for biopsy showed this to be gastric mucosa. I believe this case illustrates an esophagitis with secondary contraction pulling the stomach up into the thoracic cavity.

I agree with Dr. Benedict that the best form of treatment in benign stricture of the esophagus is dilatation. There may be some difference of opinion as to how this should be done. At the clinic we prefer to carry out dilatation over a previously swallowed thread. This ensures greater ease and safety of dilatation, and it permits the passage of dilators of greater size. In our experience, the results of this form of treatment have been highly satisfactory.

As far as surgical intervention is concerned, we find that it is seldom necessary for these patients, and I am sure Dr. Benedict and Dr. Sweet do not wish to advocate routine surgical treatment for these patients. If you look at the figures presented by the authors, you will find that even in the hands of Dr. Sweet, who is recognized as a master surgeon, the procedure is accompanied by a mortality rate of more than 5 per cent. In addition, postoperative complications have developed in more than 5 per cent of their cases. One hesitates to think how much greater the risk and complications would be in the hands of a less experienced surgeon. I feel that as a rule we should exercise every care to treat these patients by means of dilatation, and that we should employ surgery only for those whose condition will not respond to dilatation.

## GASTRIC POLYPS

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### INTRODUCTION

Benign tumors of the stomach are comparatively rare. Their reported incidence varies, depending upon the source of statistics. Eusterman<sup>1</sup> found 1.3% of all gastric tumors encountered surgically to be benign. On the other hand, Rieniets<sup>2</sup> found 34 (17%) of benign tumors (leiomyomas) in a careful survey of 200 consecutive necropsy subjects. Rigler and Erickson<sup>3</sup> report that in a survey of 6,742 autopsy cases, 194 gastric tumors were found, of which 50 (26%) were benign. The same workers found 26 (11%) benign tumors among 239 gastric neoplasms diagnosed roentgenologically. Finesilver<sup>4</sup> found only 6 benign lesions in 43,200 gastrointestinal x-ray examinations. Stewart<sup>5</sup> observed 78 benign lesions in 11,000 post mortems. Dudley et al<sup>6</sup> at Bellevue observed 32 benign lesions in 4,413 necropsy cases. They also noted that 1.3% of their cases with gastric neoplasms were benign. Similarly, Lewitan and Nygaard<sup>7</sup> also reported 1.3% of benign gastric lesions in their series of cases. Rumold<sup>8</sup> concluded that only 1% of all tumors of the stomach are benign. Carey and Hay<sup>9</sup> recently reported on 80 gastric polyps encountered during gastroscopic examination from 1936 to 1947. Schindler<sup>10</sup> observed 1.5 to 2% of benign neoplasms in patients subjected to gastroscopy. The direct observation of the stomach by gastroscopy has uncovered benign tumors of the stomach in numbers closely approaching their actual incidence indicated by autopsy.

Benign tumors of the stomach are significant clinically because they may be the cause of symptoms for mechanical reasons or may present gastro-intestinal symptoms. They may bleed, and, though their malignant potentialities have not been clearly defined, by analogy with polyps of the colon, a significant percentage of adenomatous polyps of the stomach may be expected to eventuate in carcinomas.

It is the purpose of this report to compare the accuracy of gastroscopy and roentgenography in the diagnosis of polypoid lesions of the stomach and to correlate the presence of atrophic and/or hypertrophic changes in the gastric mucosa, and the presence or absence of acid, with their occurrence.

The material for this study is made up of 62 patients on whom an adequate follow-up was possible out of a group of 70 patients in whom gastroscopic examination disclosed one or more polypoid lesions. They were culled from a

series of over 4,000 gastroscopic examinations performed from 1940 to 1948 at the Cook County, Illinois Central and Henrotin Hospitals in Chicago. The lesions varied from a few mm. to 3-4 cm. They have been divided into three groups for the purpose of study: those which were considered to be benign on gastroscopic examination—those in which the diagnosis as to benignity or malignancy was not made by gastroscopic examination—and those which were looked upon as being malignant. The follow-up was based upon the gross and microscopic examination of the surgically excised specimens or on the appearance of the lesion on reexamination and the clinical course of the patient.

Polyps were considered benign if the mucosa covering them had the same coloring as the surrounding mucosa, if they were smooth, not nodular, and frequently pedunculated. Occasionally the dome of the polyp appeared paler than the surrounding mucosa. Polyps considered as possibly malignant were uneven, nodular, often sessile, and the mucosa covering the polypoid masses usually had whitish or grey cobweb-like streaks running through it and was paler than the surrounding mucosa. A definite tendency to bleed was noted. Only in one instance of a polypoid lesion of the antrum did the mass assume a cauliflower-like appearance, with the attached base smaller in diameter than the rest of the polyp. In this instance a definite diagnosis of a malignant polyp was made and proven surgically. Polyps which appeared edematous, somewhat larger than the usual pea-sized lesions, and covered with mucosa redder than normal and occasionally showing superficial mottling were considered gastroscopically as indeterminate.

#### **COMPARISON BETWEEN X-RAY, GASTROSCOPY AND SURGERY. (TABLE I)**

Benign polyps were diagnosed gastroscopically in 20 patients. The x-ray was negative in 56.2% of them; a polyp was reported in only 5%; and filling defects in the remainder. Of these 20 patients, four were operated upon. Three (75%) had benign polyps on histologic examination, one had a hypertrophic gastritis only. The remainder have not been operated upon but have continued under observation for periods of two months to four years.

Thirty patients were diagnosed gastroscopically as possibly having malignant polypoid lesions. In these 30 patients the x-ray was negative in 28.5%, a polypoid lesion was diagnosed in two, and a diagnosis of filling defects or tumors were made in the remainder. Fourteen of these 30 patients were operated, with histologically benign lesions in four (two benign polyps, one hypertrophic gastritis and one tuberculosis of the stomach) and malignancy in ten (71%) of them. The x-ray was negative in three of the proven malignant cases, but positive in all four patients with benign lesions. The unoperated patients were observed for periods of one month to two years. During this time one patient who was under treatment for pernicious anemia died, but no post mortem was obtained, so that the gastroscopic observation was not definitely evaluated.

In 12 patients the gastroscopic diagnosis was indeterminate, and in these the x-ray was negative in 30%. Five of these were operated upon. In one (20%) of them the only lesion found was hypertrophic gastritis, in two (40%) benign polyps, in one (20%) both a benign and a malignant polyp, and in one (20%) a malignant polyp. Two of the seven unoperated patients have been repeatedly observed gastroscopically, but no changes noted. The others have been observed clinically and no additional changes in the patients have been noted.

Polyoid growths were found in 19 of the 23 operated patients. In seven of them the polyps proved to be benign, in 11 malignant, and in one there was a benign and a malignant polyp. Of the seven patients with benign lesions, one had a single and six multiple polyps. Of the 11 patients with malignant lesions, nine had a single and two had multiple polyps.

Comparing the diagnostic accuracy of gastroscopic and roentgenologic examinations, we find that the latter was negative in 38.2% of the gastroscopically diagnosed lesions and in 28% of the surgically proven cases. This demonstrates the value of gastroscopy in supplementing x-ray examination of patients with gastric symptoms.

#### AGE, SEX AND RACE DIFFERENCES. (TABLE I)

The highest incidence of gastric polyps occurred in the higher age groups, 70% of the patients belonging in the sixth and seventh decade. Only one patient was below 30 years.

In our series of patients the males predominated two to one, 72% being male and 28% female. Similarly, only 30% of these tumors were found in colored patients, although the percentage of colored patients is quite high in the Cook County Hospital.

A normal mucosa was found in 75% of the benign, in 75% of the indeterminate, and in 78.5% of the malignant cases. Findings characteristic of atrophic gastritis were present in 20% of the benign, 8.3% of the indeterminate, and 17.8% of the malignant. Findings characteristic of hypertrophic gastritis were noted in 5% of the benign, 16.6% of the indeterminate, and 3.5% of the malignant cases. Achlorhydria was found in 71.4% of the benign, 75% of the indeterminate, and 73.3% of the malignant cases. Hyperchlorhydria was found in *none* of the benign or indeterminate group and in only 13.3% of the malignant group. Normal values were found in 28.5% of the benign, 25% of the indeterminate, and 13.3% of the malignant group. Of the histologically proven benign polyps, all had a normal mucosa, 80% had an acidity and 20% a hyperacidity. Of the histologically proven malignant polyps, 81.8% had normal mucosa, 0% hyperacidity, 14.2% a normal acidity, and 85.7% had an achlorhydria.

## DISCUSSION

In confirmation of the reports by others, we too found that over 38% of polypoid lesions will not be diagnosed by x-ray examination alone. The failure to diagnose these lesions is more common in the small benign ones than

TABLE I  
*Clinical Data in a Series of Patients with Polypoid Lesions of the Stomach*

CLINICAL DATA	PERCENTAGES				
	Gastroscopic Diagnosis			Histologic Diagnosis	
	Benign	Indet.	Malig.	Benign	Malig.
<i>Sex</i>					
Female.....	35	8.3	20	11.1	16.6
Male.....	65	91.6	80	88.9	83.4
<i>Age Group</i>					
Below 50.....	26.6	33.3	16	28.5	11.1
Above 50.....	73.3	66.6	84	71.4	88.8
<i>Race</i>					
White.....	66.6	66.6	72	57.1	66.6
Colored.....	33.3	33.3	28	42.8	33.3
<i>Number of Polyps</i>					
Single.....	50	42.8	62.5	14.2	81.8
Multiple.....	50	57.3	37.5	85.7	18.1
<i>Gastric Mucosa</i>					
Atrophic.....	20	8.3	17.8	—	9.09
Hypertrophic.....	5	16.6	3.6	—	9.09
Normal.....	75	75	78.5	100	81.8
<i>Gastric Acidity</i>					
Achlorhydria.....	71.4	75	73.3	80	85.7
Hyperchlorhydria.....	—	—	13.3	20	—
Normal ranges.....	28.5	25	13.3	—	14.2
<i>X-ray Findings</i>					
Negative (lesion not seen).....	56.2	30	28.5	28.5	27.2
Positive (polyp or filling defect reported).....	43.8	70	71.5	71.4	72.7

in the larger malignant ones (56.2% and 28.5% respectively). This observation makes gastroscopy almost imperative in patients who have gastrointestinal complaints but who have negative x-rays. Thus, in this series all but two of the benign and four of the malignant group had complaints of pain and nausea. Some complained of vomiting and a lesser number of anorexia. Hematemesis occurred in two of the benign and in one of the malignant group.

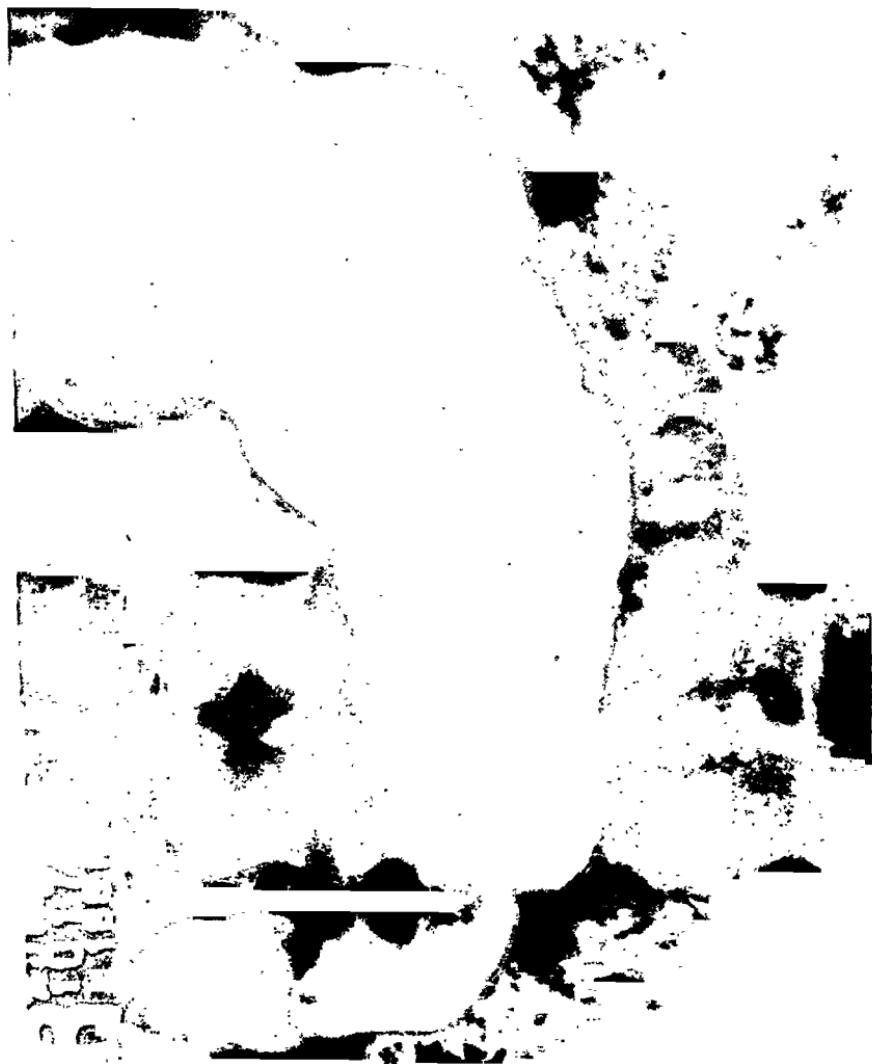


FIG. 1. Roentgenogram showing punched-out filling defect near the pylorus which gastroscopically appeared to be distal to the pyloric sphincter.

Yet in over 38% of them the x-ray was negative. Gastroscopic examination should also be done in patients with primary anemia and in anemia of unexplained origin because of the high incidence of polyps and occasional malignancy in this group<sup>12</sup>.

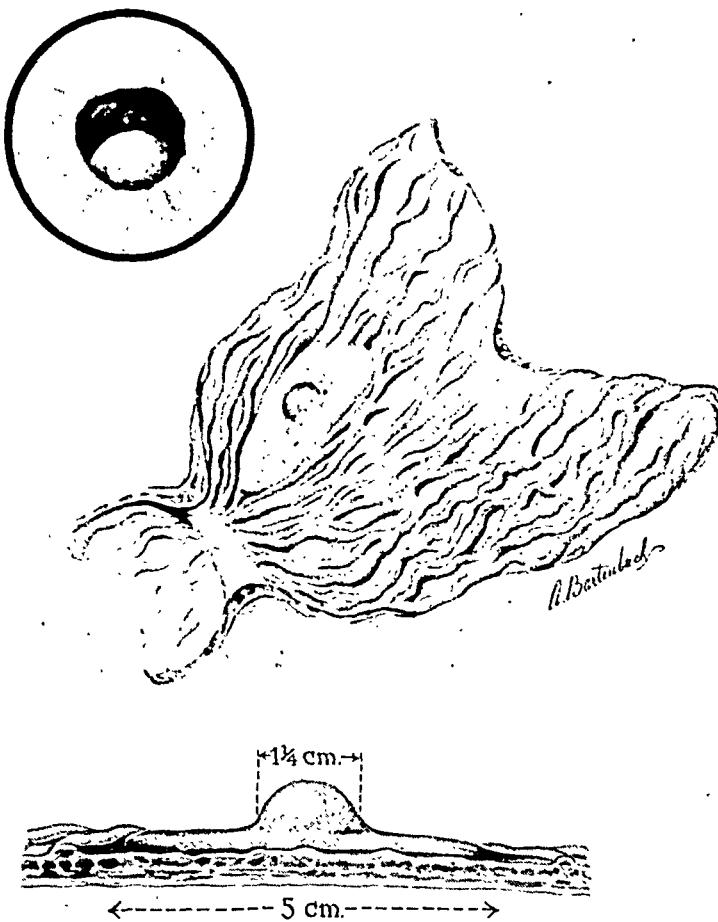


FIG. 2. Artist's drawing of (a) gastroscopic appearance of the polypoid lesion shown in Fig. 1, (b) appearance of resected stomach showing the polypoid lesion close to the pylorus, and (c) cross section of the stomach near the polypoid lesion.

While the gastroscopic examination will reveal a much higher percentage of polypoid lesions than the x-ray examination, it nevertheless has certain drawbacks. In many instances it was difficult to state definitely from the gastroscopic appearance alone whether the lesion was benign or malignant, and diagnostic errors were made (Table I). At times while the polyp is visualized, its gastroscopic description as to size, location and attachment (i.e. whether pedunculated or sessile) were at variance with the findings at operation. Thus in one of our patients diagnosed as having a pedunculated polyp in the duo-

denum protruding through the pylorus, the neoplasm proved, at operation, to be a sessile myoma of the antrum (Fig. 1 and 2). Finally, gastric polyposis may be confused with marked hypertrophy of the rugal folds, which, in their edematous state, resemble polyps (Fig. 3). Occasionally the folds surrounding a gastric ulcer have a polypoid enlargement of the rugae. Such mistaken identity has occurred in our material three times, and others have had the same experience<sup>13, 14</sup>.



FIG. 3. Gastroscopic appearance of the stomach in a patient with marked hypertrophic gastritis and pseudopolypoid formation in one of the folds.

The surgical findings too do not always point to the accurate diagnosis. In certain instances the pathologist is unable to tell from the gross specimen the nature of the lesion.

The data in Table I demonstrates that the gastroscopic observations of the stomach mucosa and the determination of the gastric acidity are of comparatively little help in the differentiation between benign and malignant lesions. These observations therefore are of very limited value in the differential diagnosis of polypoid lesions of the stomach.

The recently well accepted test for carcinoma, i.e. the examination of sediment from secretions from various body cavities, may be a helpful supplemental diagnostic procedure. Its value has recently been demonstrated in one of our



FIG. 4. Tissue obtained by gastric aspiration showing irregular, large tortuous glands which are lined chiefly by goblet cells with large nuclei having granular chromatin and rather prominent nucleoli. In the deeper layers an occasional mitotic figure is seen with some irregular arrangement of the nuclei. At some points actual invasive qualities were noted. The stroma is vascular, infiltrated with eosinophils and plasma cells. Diagnosis of polypoid tumor was made with questionable malignancy.

patients in whom the x-ray was negative, but because the gastric sediment contained a small piece of tissue which was diagnosed as gastric polyp, suspiciously suggesting malignancy, gastroscopy was done (Fig. 4). Four polyps were found and diagnosed as possibly malignant, but proved to be benign after surgical excision (Fig. 5) and histological examination (Fig. 6).

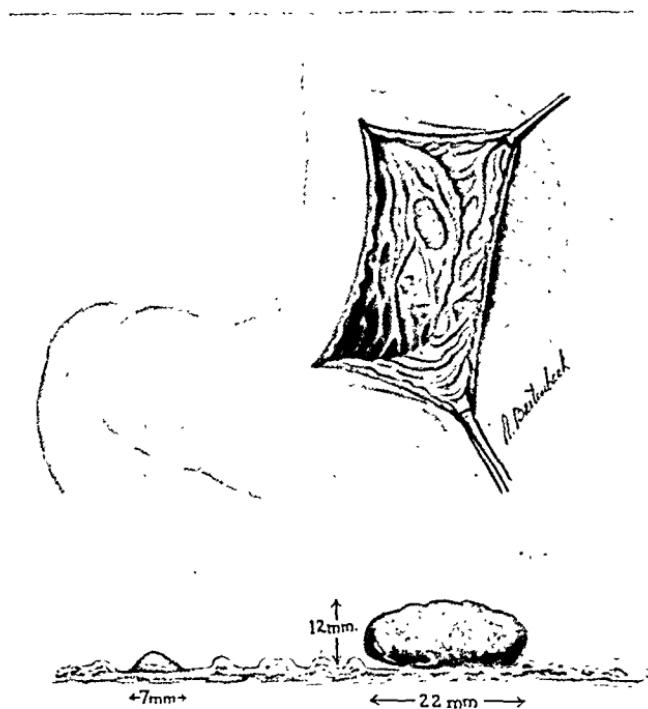


FIG. 5. Artist's drawing of stomach—negative on x-ray examination—showing one large and three smaller polyps (on gastroscopic examination) and also at operation. Lower figure shows cross section of the stomach wall with approximate size of larger polyp and its relation to the smaller ones.

In reviewing the whole series of patients it appears that gastroscopic examination of patients with definite gastrointestinal symptoms but with negative x-ray findings may reveal in quite a few of them some type of polypoid growth. These growths have at times no definite characteristic criteria as to their malignant or benign nature. Most of them, regardless of the later proven diagnosis, had no free acidity on the test meal and most had a normal mucosa, so that deviation from the normal in such patients is without diagnostic significance. A safe method for dealing with polyps of the stomach therefore appears to be surgical removal of these lesions.



FIG. 6. Section of the small polyps varied in appearance. They generally consisted of low mounds of mucosa projecting from the surface, the glands of which were slightly irregular in outline, but retained mature quality in most instances. Some of the glands were dilated and the stroma appeared rather edematous. The section of the large poly was somewhat variable, the glands were moderate in number, tortuous, and irregular, and in areas answered to the description above for the tissue found in the gastric contents. There was some hemorrhage, especially superficially into the stroma and the stroma was everywhere markedly edematous and irregularly infiltrated with eosinophils and plasma cells, and occasional neutrophils. Diagnosis was glandular polyps of the stomach.

## SUMMARY AND CONCLUSION

1. The incidence of gastric polyposis has been discussed based on clinical, gastroscopic, x-ray and surgical observations.
2. X-ray fails to reveal these lesions in almost 40% of the cases in which polyps were seen upon gastroscopic examination. In about one-third of the patients, however, no definite diagnosis of the malignancy or benignancy of the lesion was made.
3. Presence or absence of free acid and the appearance of the mucosa has in our material not been correlated well with the symptoms nor with the final diagnosis of the lesion.

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## THE SURGERY OF COMPLICATIONS OF ULCERATIVE COLITIS

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### INTRODUCTION

The progressive nature of ulcerative colitis provides our most difficult problem in surgical management. The course of the disease even after fecal diversion is often explosive and unpredictable. Tissue repair is compromised. Post-operative complications are frequent and require endless hours of care and attention. We are therefore delighted when the skill and perseverance of the gastroenterologist combine to arrest progression and render the patient economically and socially fit. In a considerable group, however, such a regimen fails or complications of the disease appear, and surgical intervention is imperative. Many misconceptions still exist with regard to this surgery. We wish to consider some of these false impressions in the light of recent experience.

### SURGERY—THE MORTALITY AND THE HANDICAP IT IMPOSES

Delay in surgical intervention is frequently justified on the basis of a forbidding mortality and the belief that ileostomy dooms the individual to a life of restricted activity. For example, it has been stated that for the young woman "an ileostomy is a complete frustration and denial of all romance, marriage, and bearing of children". These are misconceptions. The surgical mortality of ileostomy in clinics with considerable experience in the management of the disease is currently less than 5 per cent,<sup>1</sup> and the mortality for colectomy is even less. In a recent series (Table 1) we had 3 deaths in 69 consecutive procedures for complicated ulcerative colitis. One of these was avoidable. Recent advances in anesthesiology, the use of antibiotics and chemotherapy, the availability of large quantities of blood and blood substitutes, and an increasing understanding between gastroenterologist and surgeon are responsible for this reduction in mortality. These adjuncts in surgical treatment permit a bolder approach to major complications with reasonable safety. We now consider many of these desperate cases too sick not to operate upon.

The handicap of an ileostomy has likewise been to a great extent eliminated. With the Koenig-Rutzen type of ileostomy bag<sup>2</sup> the average patient is able to assume fairly normal economic and social activity. Several of our young female patients have married after establishment of ileostomy. Two have borne normal children. All have apparently made a satisfactory marital ad-

justment. Most enjoy a normal life. Ileostomy is not sufficiently undesirable to warrant delaying surgery when indications are present. Procrastination causes ulcerative colitis deaths.

#### COMPLICATIONS REQUIRING IMMEDIATE SURGERY

1. Perforation
2. Uncontrolled Hemorrhage
3. Obstruction

These life-threatening complications occur after diversion of the fecal stream as well as in the actively functioning colon. Ileostomy, therefore, offers no

TABLE 1  
*Surgical Mortality of Ulcerative Colitis*

PROCEDURE	CASES	DEATHS	MORTALITY %
Ileostomy.....	28	1*	3.5
Proximal colostomy.....	2	0	0
Ileo-sigmoidostomy.....	2	0	0
Proximal colostomy plus partial colectomy.....	2	0	0
Ileostomy plus partial colectomy. 1 Stage.....	3	1**	33
Colectomy (abdominal)			
a. Partial.....	11	0	0
b. Ileum to mid-sigmoid.....	12	1***	8
Combined abdomino-perineal resection sigmoid and rectum.....	7	0	0
Combined abdomino-perineal resection left colon and rectum.....	2	0	0

3 deaths in 69 consecutive procedures.

\* Death from Acute Fulminating Ulcerative Colitis.

\*\* Death from Perforation Ileum by Ileostomy Tube.

\*\*\* Death from Thrombosis Vena Cava and left iliac vein with pulmonary emboli, and hemorrhage from gastric ulcers.

insurance against their appearance. Through the years the idea has developed that these patients are usually too sick to withstand major surgery; that the mortality of operation in free perforation and massive uncontrolled hemorrhage approaches 100 per cent; that colectomy should not be done as an emergency procedure with a patient in desperate condition but reserved for chronic cases. We believe that radical surgery has a place in the treatment of uncontrolled hemorrhage and free perforation. If ileostomy is not adequate, colectomy should be rapidly effected. These patients are too sick not to be operated upon.

Obstruction from the acute inflammatory process alone or later stricture formation may precipitate a proximal perforation. For this reason obstruction of even the defunctionalized colon is an indication for prompt surgery. The

practice of closing the distal ileal stump after ileostomy and dropping it back in the abdomen is fraught with danger. It should be exteriorized as a mucous fistula in anticipation of distal obstruction.

Uncontrolled bleeding from the colon is not generally recognized as an indication for surgical intervention. As in active bleeding from peptic ulcer, operation should be deferred if possible. When continued blood replacement can barely keep up with blood loss more definitive treatment must be employed.



SEROSAL VIEW

MUCOSAL VIEW

FIG. 1. Case 1. Colon removed as an emergency procedure from terminal ileum to mid-sigmoid. A large perforation is visible in the cecal area on the left. There is marked destruction of the mucous membrane and extensive polypoid changes.

Two recent experiences with emergency problems of this type will serve to illustrate certain of these points.

*Case 1.* R. G., female, 30 years. Duration of Disease:  $4\frac{1}{2}$  years. Hospitalized 10/8/47 with intensive medical treatment in hospital until 1/24/48. Elective Ileostomy 1/24/48, disease intractable and progressive. 1/31/48 Change in clinical picture; onset of fever, back pain, abdominal pain, high leukocytosis. 2/8/48 Mass in R.U.Q. abdomen noted; question of hepatitis. 2/10/48 to 2/13/48 Repeated massive hemorrhages from rectum and mucous fistula associated with shock. Measured blood loss from colon 4000 cc. in 48 hours. 2/13/48 Change in clinical picture—Signs of spreading peritonitis—bleeding from rectum and mucous fistula of distal ileum stopped. 2/14/48 Rapid emergency colectomy from terminal ileum to mid-sigmoid—patient in desperate condition with a distended, rigid abdomen, and

the facies of peritonitis. 4 liters of blood and pus aspirated from peritoneum. Free perforation of cecum present. Peritonitis generalized.

Recovery.



FIG. 2. Case 2. Survey film of abdomen showing roentgen evidence of an obstructed right colon due to inflammatory edema and kinking at splenic flexure. Proximal perforation developed.

The accompanying illustration, Fig. 1, shows the advanced degree of local disease in the colon.

#### COMMENT

This patient illustrates certain significant points:

1. Ileostomy does not always prevent progression of the disease; in this case per-

foration and massive hemorrhage appeared shortly after the colon was defunctionalized.

2. When the clinical picture in ulcerative colitis changes, the local pathology changes. Perforation is often masked and the diagnosis made difficult by the frequency of fever, abdominal tenderness, pain and muscle guarding in the course of non-perforating disease. A rapidly rising leukocyte count is suggestive.

3. There is a close relationship between hemorrhage and perforation. Both indicate deep destruction of the bowel wall.

4. Emergency colectomy for exsanguinating hemorrhage and perforation with peritonitis was successfully carried out in a critically ill patient. Without it the patient would undoubtedly have died.

*Case 2.* B. S., male, 46 years. Duration of Disease: 2 years. Hospitalized: 10/4/47—Acutely ill, anemic, and bleeding. Intensive medical treatment: 10/4/47 to 11/6/47. Downhill course—repeated massive hemorrhages and episodes of shock; passed clots of blood that looked like casts of the bowel; emergency transfusions. Condition desperate at all times. 11/8/47 Perforation proximal colon; spreading peritonitis secondary to an acute inflammatory obstruction at the splenic flexure. (Fig. 2) Emergency ileostomy; perforation sealed. 11/21/47 to 11/24/47 Hemorrhages—500 to 1000 cc. daily; patient rapidly growing worse. 11/24/47 Emergency colectomy; ileum to sigmoid; recovery.

Blood replacement required during hospitalization: 21,000 cc. whole blood, 4,000 cc. plasma, 6,000 cc. plasma equivalents of concentrated serum albumin.

#### COMMENT

This case illustrates:

1. Obstruction of the colon may occur during the acute stage of the disease from edema and angulation.

2. Obstruction is a factor in proximal perforation of the colon.

3. Ileostomy does not always prevent further complications in the defunctionalized colon.

4. The close relationship between massive hemorrhage and perforation.

5. The favorable outcome of emergency surgery and treatment in a patient dying from profuse uncontrolled hemorrhage in which every conservative adjunct had been exhausted.

If patients such as these can survive emergency colectomy, surgery should no longer be so formidable for the average complications of ulcerative colitis. These are examples of what concerted surgical effort has to offer these desperately ill patients today.

#### COMPLICATIONS REQUIRING ELECTIVE SURGERY

1. Polyposis
2. Granulomata

3. Neoplasm
4. Fistulae and Sinuses
5. Intractable secondary complications such as arthritis, iritis, etc.

The recurrent cycle of remission and relapse in ulcerative colitis is attended by tissue destruction and repair. The colon frequently develops a pseudopoly-poid lining or a lumen lined by granulation tissue with only traces of abnormal epithelium remaining. Malignancy is prone to develop in this abnormal epithelium. Cattell<sup>1</sup> reports malignancy in 7 per cent of all patients who have been operated upon. Furthermore, of the group of patients who had the disease for 9 years or more, 1 in 3 has developed carcinoma. This type of carcinoma is highly malignant and frequently multiple.

Any colon which shows polyposis or irreversible mucosal changes over a period of time should be removed. Any inflammatory mass or granuloma associated with the colon should likewise be removed since it is impossible to distinguish such a lesion from carcinoma by gross examination. Colectomy should not be delayed for long periods of time in the presence of these complications. Finally, any colon defunctionalized by ileostomy should be observed periodically. If no indication for colectomy exists, barium enemas and sigmoidoscopic studies should be made from time to time to detect early evidence of complications. Only in this way can the threat of this rapidly metastasizing tumor be removed.

#### SUMMARY

1. The surgery of ulcerative colitis and its complications need no longer be associated with a high mortality.
2. Ileostomy is compatible with relatively normal social and economic activity.
3. Emergency colectomy is feasible in the treatment of certain cases of perforation and uncontrolled hemorrhage.
4. Colectomy is indicated in the presence of long-standing irreversible mucosal changes, polyposis, granulomatous masses, carcinoma and obstructive lesions.
5. Any defunctionalized colon should be observed periodically for the early detection of complications.

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## STUDIES WITH BROMSULPHALEIN

### I. ITS DISAPPEARANCE FROM THE BLOOD AFTER A SINGLE INTRAVENOUS INJECTION\*

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#### INTRODUCTION

Studies on the fate of bromsulphalein in man were undertaken to obtain more information on the rate and character of its removal from the blood, to evaluate the roles of several possible uptake sites, to assess its adequacy as a tool for the measurement of hepatic blood flow,<sup>1</sup> and to explore the possibility that certain hepatic functions could be subjected to quantitative analysis. To this end, a number of methods were employed to investigate the effect of giving bromsulphalein by single injection or by constant infusion under various conditions. The results will be described in a series of papers. This report presents observations made on the disappearance of bromsulphalein in health and disease following a single intravenous injection of the dye.

#### METHODS

All subjects are given a standard dose of 150 mg. bromsulphalein per square meter of surface area. Surface area is used to determine the size of the dose, for this measurement appears to be preferable to weight as an index of blood volume and probably of liver size. It does not seem reasonable, for example, to give a short, obese woman aged 45 and weighing 180 pounds nearly twice as much bromsulphalein as she would have received when she weighed 100 pounds at the age of 20. The figure 150 mg. per square meter is an arbitrary choice: since the average plasma volume of a normal person is roughly 1500 ml. per square meter of surface area, a dose of this size should result in a concentration of 10 mg. per 100 ml. plasma if a homogeneous diffusion of bromsulphalein were possible immediately after its injection.

Samples of venous blood are drawn (using some vein other than the one used for injecting bromsulphalein) at intervals of 6, 12, 20 and 30 minutes after injection of the dye. Precise timing and minimal venous stasis are observed in the collection of samples. If samples are taken within 5 minutes of injecting

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bromsulphalein, the dye may be inadequately mixed in the plasma. Samples taken more than 30 minutes after injection may contain so little bromsulphalein that determination of the dye concentration is not possible by our methods.

The concentration of bromsulphalein in the serum is measured by a method described and briefly discussed elsewhere.<sup>1</sup> As was pointed out, the method is not free from error inasmuch as recoveries from serum containing added amounts of bromsulphalein average about 0.1 mg. per 100 ml. less than the known concentrations. This loss probably occurs because alkalization with NaOH decreases the turbidity of serum and changes hemoglobin from a red to a green pigment. Hence turbidity and hemoglobin produce a greater barrier to the passage of light before than after alkalization, and the photoelectric reading of bromsulphalein is falsely low by an absolute amount which depends on the turbidity and hemoglobin concentration of the serum. A better method of bromsulphalein analysis is therefore desirable, but up to now we have not found one that retains simplicity and possesses a significantly greater accuracy. All methods using protein precipitation (acetone, alcohol, ethyl phosphate, trichloracetic acid, and salting out techniques) yield recoveries that are erratic and far less than the known amounts added. The second method of Gaebler<sup>2</sup> yields recoveries which are as accurate, and, in hemolyzed sera, more accurate than those obtained by our method. On the other hand, Gaebler's second method makes a standard correction for turbidity and hemolysis irrespective of the amount of interfering substance present. For this reason, the direction of his error (i.e. whether plus or minus) is unpredictable, and we have continued to use our method, which is more rapid, and produces a unidirectional error.

After the concentrations of bromsulphalein are determined, the logarithms of the values obtained are plotted against time. A rectilinear relationship is said to exist if a straight line can be fitted to the plotted values in such a way that none of the points deviates from the line by more than 0.2 mg. per 100 ml. The slope of the line is then determined by the following equations:

$$(1) \ C_2 = C_1 (d)^{t_2 - t_1}$$

$$(2) \ (t_2 - t_1) (\log d) = \log \frac{C_2}{C_1}$$

$$(3) \ 1 - d = \text{PDR}$$

where  $C_1$  is the concentration of bromsulphalein at time  $t_1$ ,  $C_2$  the concentration at time  $t_2$ , and PDR the percentage rate at which bromsulphalein is disappearing. For practical purposes, a time interval ( $t_2 - t_1$ ) of 10 minutes is usually employed. Whenever a straight line relationship for the four concentrations of bromsulphalein is obtained, PDR (Percentage Disappearance Rate) is cal-

culated and is expressed in per cent per minute. This terminology is slightly different from that used in previous abstracts<sup>3, 4</sup> of the work now being reported in detail.

If the line drawn between the plotted values is not rectilinear, but is curvilinear with a decreasing slope (i.e. forms a curve which tends to flatten out), the test is said to show "saturation". Under such circumstances, PDR is not constant, nor is it calculated.

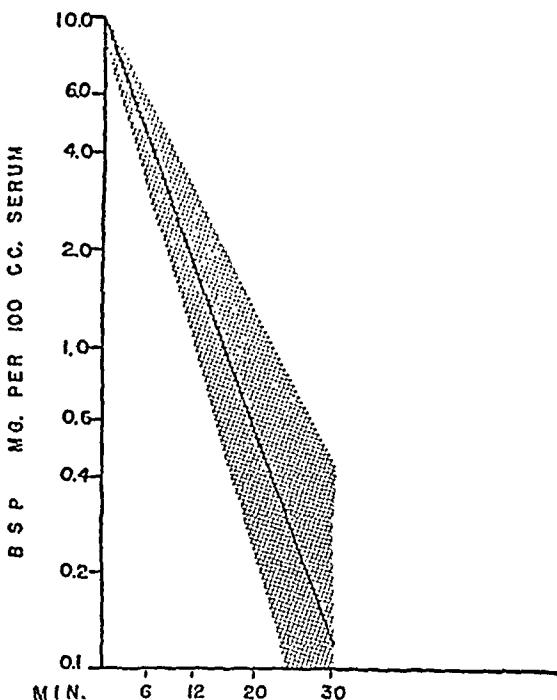


FIG. 1. PDR in healthy subjects. The line represents the average value, 13.6 per cent per minute. The shaded area indicates the total range of values obtained for PDR: 9.1 to 16.0 per cent per minute.

#### RESULTS—CONTROL SUBJECTS

Seventy-two tests were carried out in 55 healthy and ambulatory volunteers. In 66 tests (92%), a straight line relationship between time and the logarithms of the bromsulphalein concentrations was obtained. The mean PDR was 13.6 per cent per minute with a S.D. of  $\pm 1.9$  (Fig. 1).

In 58 of the tests displaying rectilinearity, the hematocrit was determined simultaneously, the blood volume was estimated according to the tables of Gibson and Evans,<sup>5</sup> and, on the assumption that an immediate and uniform distribution of bromsulphalein takes place, the theoretical concentration of the dye immediately after its injection was calculated. In 45 of the 58 cases (78 per cent) this theoretical concentration was within  $\pm 10$  per cent of the value obtained by extrapolating the straight line to 0 time.

One hundred and seven tests were carried out in 103 hospital patients who suffered from a variety of complaints, but who apparently were free from hepatic disorders. In 76 tests (71 per cent), a straight line relationship was obtained. PDR averaged  $12.8 \pm 2.45$  per cent per minute (Fig. 2). In the remaining tests, rectilinearity was not demonstrated: an irregular curve was obtained six times, and 25 tests manifested "saturation" in that the slope of the curve decreased. This decrease usually occurred between the 20 and 30

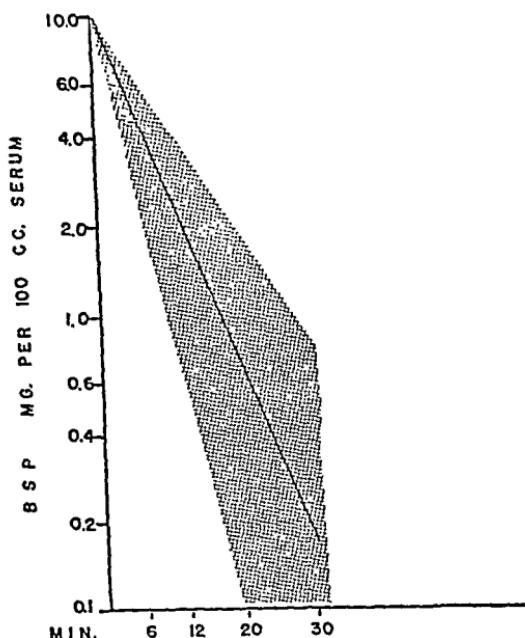


FIG. 2. PDR in hospital patients without apparent hepatic disorders. The line represents the average value, 12.8 per cent per minute. The shaded area indicates the total range of values obtained for PDR: 8.5 to 23 per cent per minute.

minute samples when the concentration of bromsulphalein was quite low (Fig. 3A), but in a few cases the curve was characterized by a very rapid initial drop followed by a progressive flattening (Fig. 3B).

In 58 cases, a straight line relationship and hematocrit determinations permitted a comparison of the theoretical concentrations of bromsulphalein at 0 time. A positive correlation within  $\pm 10$  per cent was obtained in 41 instances (71 per cent).

These observations indicate that in most healthy subjects and in the majority of patients without apparent liver disease, a constant proportion of bromsulphalein disappears from the blood per unit time. This constant proportion, called the Percentage Disappearance Rate, may be said to have a normal range extending from 10 to 16 per cent per minute. A similar constant, although of

smaller value, has been established for the disappearance of galactose by Colcher and associates.<sup>6</sup> In the case of bromsulphalein, the constant PDR is usually maintained for the first 30 minutes following injection of the dye, but in some cases, if the dye content of serum is extremely low, toward the end of this time interval, PDR may fluctuate considerably. Since a deviation of 0.2 mg. per 100 ml. is allowed by definition, however, changes in PDR of this type are disregarded, a procedure which can be defended since it applies only to low levels of bromsulphalein when more than 95 per cent of any injected dose has disappeared.

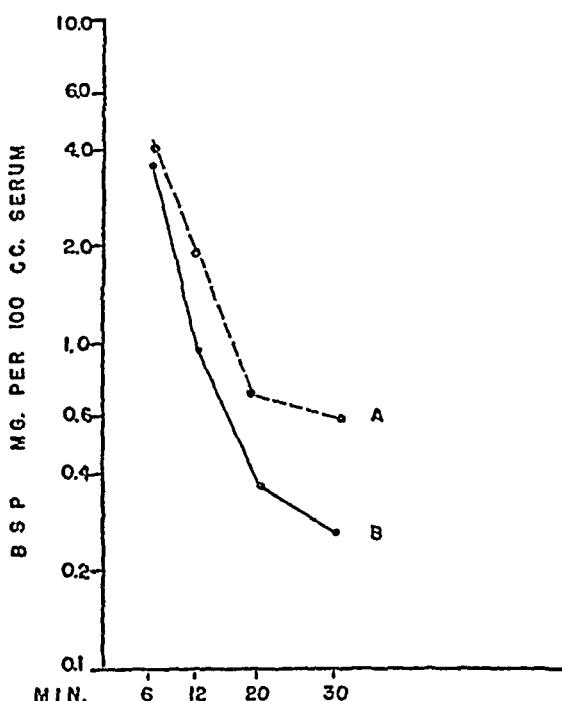


FIG. 3. Examples of "saturation" in hospital patients without apparent hepatic disorder. A is the type seen most frequently: a decrease in PDR at low levels. B is a type characterized by a very rapid PDR at the beginning of the test.

A curve which, according to definition, manifests "saturation" indicates that PDR is decreasing while significant amounts of bromsulphalein remain in the blood. A curve of this type was found in roughly one out of four hospital patients even though no clinical evidence of hepatic dysfunction was apparent. The disappearance of bromsulphalein after the 30 minute interval was not studied, but it is possible that a decreasing PDR might be found not infrequently if accurate analysis of bromsulphalein were feasible at very low concentrations.

Irregular curves with a transitory increase of slope (i.e. increased PDR) occur

very infrequently. If they do occur, they may possibly be caused by massive and spontaneous changes in hepatic blood flow, but more often irregular curves can be attributed to a technical error in sampling or analyzing the blood.

#### RESULTS—PATIENTS WITH HEPATIC DISORDERS

When the mechanisms that remove bromsulphalein from the blood are impaired, PDR theoretically can be affected in two ways: (1) PDR rapidly decreases during the 30 minute tests; i.e. saturation is pronounced; or (2) PDR is constant but has a very low value. Both those abnormal types occur in patients with hepatic disorders.

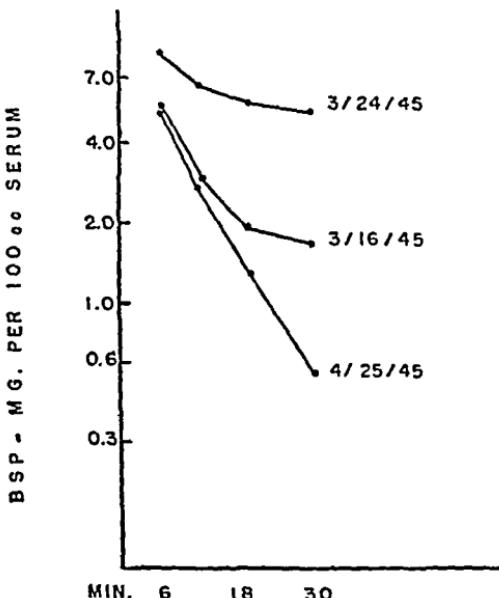


FIG. 4. Bromsulphalein disappearance in a case of infectious hepatitis. The test on 3/16/45 was carried out in the pre-icteric phase, the test on 3/24/45 at the height of the jaundice, and the test on 4/25/45 after clinical recovery. PDR on 4/25/45 is 19.4 per cent per minute.

In patients with jaundice (excepting the hemolytic or "prehepatic" variety), a rapidly decreasing PDR, indicating marked "saturation" was found (Fig. 4). As might be expected, the shape of the curve gave no indication as to the cause of the jaundice. The most intense saturation (curves characterized by an almost complete absence of bromsulphalein disappearance between the 20 and 30 minute blood samples) was usually found in patients with the most intense jaundice, such as patients with severe hepatitis or with neoplastic obstruction of the common duct. On the other hand, similarly intense saturation occasionally appeared in non-icteric patients. Fig. 5 presents three examples of

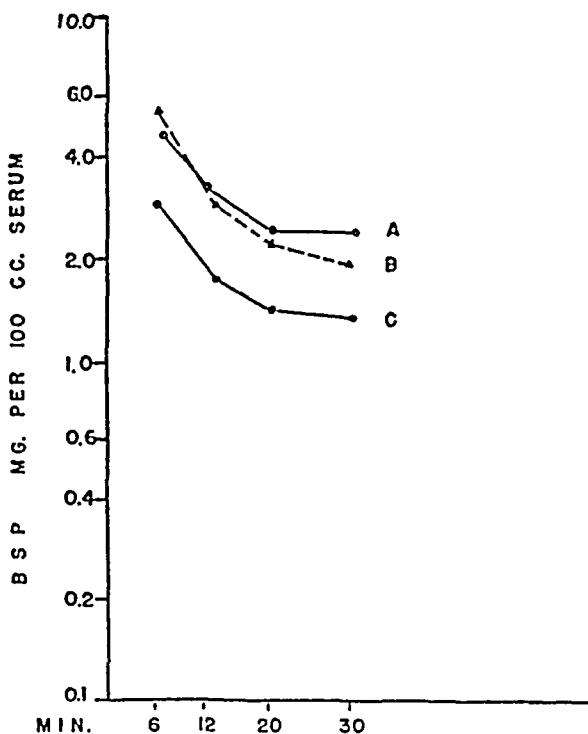


FIG. 5. Three examples of a rapid decrease in PDR in non-icteric patients. A. Infectious mononucleosis. B. Severe hyperthyroidism. C. Miliary tuberculosis of liver.

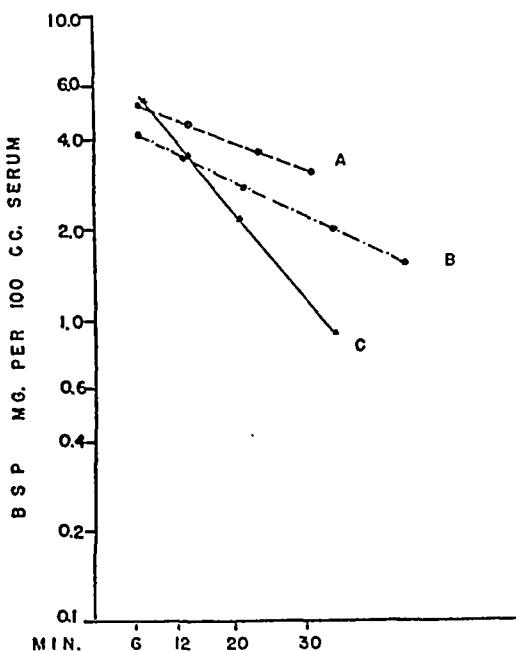


FIG. 6. Examples of bromsulphalein disappearance in 3 cases of cirrhosis. Cases A and B had advanced cirrhosis with PDR values near 2 per cent per minute. The cirrhosis in case C was quiescent; PDR is 6.4 per cent per minute.

this type: a non-jaundiced case of infectious mononucleosis, a case of severe thyrotoxicosis, and a case of miliary hepatic tuberculosis.

Following recovery from infectious hepatitis, the "saturation" phenomenon disappears within 1-3 months (Fig. 4). Of 16 patients who were tested 3-24 months after an attack of clear-cut hepatitis, 2 showed mild "saturation", and 14 had a constant PDR averaging 11.9 per cent per minute. Two patients with severe hepatitis, however, had PDR values of only 7.2 and 7.4 per cent per minute one year later, although both were clinically well at that time.

A bromsulphalein disappearance characterized by a constant but abnormally slow PDR was found frequently in patients with hepatic cirrhosis and oc-

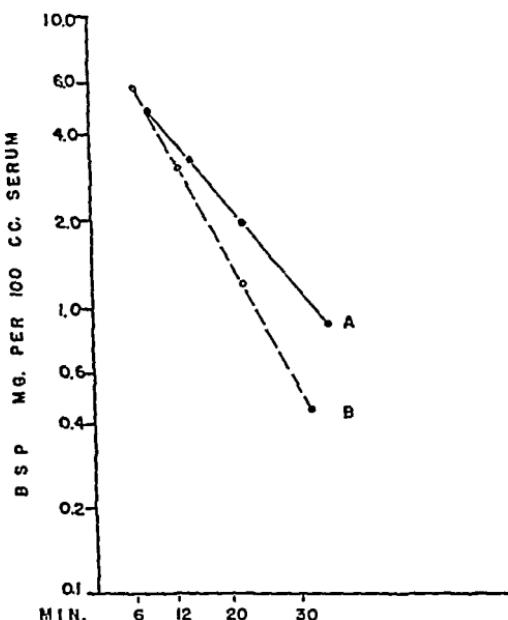


FIG. 7. Bromsulphalein disappearance during congestive failure (A) and after recovery (B). As was true of a number of patients with congestive failure, PDR was constant.

casionally in patients suffering from congestive failure. Of 46 tests carried out in 31 cases of cirrhosis, 35 (24 patients) were characterized by a constant PDR of the type shown in Fig. 6. The lowest PDR was 1.9 per cent per minute, the highest 8.2 per cent, and the average for the group of 35 tests, 3.9 per cent per minute. Extrapolation of the straight line to 0 time yielded a value considerably less than 10 mg. per 100 ml., as might be expected in view of the increased plasma volume of cirrhotic patients. Extension of the test beyond the 30 minute period, an infrequent procedure, showed that a constant PDR could be maintained for 45-90 minutes. In 11 tests, of which 5 were carried out in

jaundiced cirrhotics, saturation was evident, and the curves could not be distinguished from those obtained in severe cases of hepatitis.

PDR in 19 patients (28 tests) with congestive failure was abnormal but its character was quite varied. "Saturation" was frequent, but a slow, constant PDR (average: 7.0 per cent per minute) was obtained 16 times in 12 patients. An example of this type, with tests carried out before and after successful treatment of congestive failure, is shown in Fig. 7.

In some instances, a very interesting phenomenon occurred, namely a high constant PDR. As shown in table I, the diagnoses in the 12 patients who had a PDR over 17.7 per cent are quite varied. The patient with nephrotic syndrome did not lose excessive bromsulphalein in his urine. A rather unexpected

TABLE I  
*Cases Showing Very Rapid PDR*

CASE	DIAGNOSIS	PDR
M. D.	Functional G-I. Disease	21.0
I. DeF.	Fatty Infiltration of Liver	20.0
M. S. H.	Nephrotic Syndrome	23.0
C. D.	Pycelonephritis, chronic	20.0
R. K.	Diabetes mellitus	18.7
W. N.	Post-Infectious Mononucleosis	18.6
W. C.	Fatty Infiltration of Liver	22.5
D. C.	Fatty Infiltration of Liver	20.0
M. St. J.	Fatty Infiltration of Liver; Hypertension	18.5
M. C.	Fatty Infiltration of Liver	21.0
C. V. K.	Hemolytic Anemia	17.8
R. P.	? Little's Disease	20.8

feature is that the list includes patients who, on clinical grounds, were suspected of having mild forms of hepatic derangement. These patients gave a history of alcoholism and presented a smooth, enlarged liver which improved rapidly with therapy.

#### DISCUSSION

In the interpretation of blood volume studies by the Evans blue dye method, considerable argument has prevailed concerning the point at which mixing can be assumed to be complete. Some authors feel that diffusion of Evans blue into relatively stationary layers of plasma may take 20 minutes.<sup>7</sup> It has also been assumed that adequate mixing of bromsulphalein takes an interval of this length.<sup>8</sup> Evans blue, however, is a colloidal dye which disappears slowly from the blood. Bromsulphalein is a soluble and dialyzable substance<sup>9</sup> which dis-

appears rapidly.\* Our assumption that bromsulphalein is adequately mixed 5 minutes after its injection is supported by the facts that PDR frequently is constant after the 6 minute sample, and that extrapolation to 0 time of the straight line fitted to the plotted values gives reasonable figures for bromsulphalein concentration.

The existence of a constant PDR for bromsulphalein in many normal subjects permits, in fact, certain general inferences concerning the mechanisms responsible for the dye's removal. If the disappearance of bromsulphalein after the first 5 minutes were affected by a series of different processes, i.e. first a diffusion into stagnant, peripheral layers of plasma, then an uptake by the R-E system, and finally a removal by liver cells, the chances of obtaining a constant PDR would be exceedingly slight. Hence it would seem that the disappearance of bromsulphalein is conditioned either (1) by a number of processes all acting simultaneously and equally over a period of 30 minutes; or, as seems far more likely, (2) by one paramount mechanism which usually is so efficient that the contributions of other mechanisms are obscured. If this is the case, 'saturation' may be caused by impairment of the primary removal mechanisms or by undue prominence of secondary mechanisms.

The constant PDR found in a number of patients with cirrhosis or with congestive failure may indicate that a secondary mechanism has replaced a relatively non-functioning primary process, but the problem is complicated by the changes in hepatic blood flow that occur in the cirrhotic and in the congested liver. In any case, the constant PDR of cirrhosis is another strong argument against the hypothesis that the mixing process affects the disappearance of bromsulphalein significantly after the first five minutes. If prolonged mixing were a significant factor, it should at least affect the very slow PDR of patients with hepatic cirrhosis.

The literature presents conflicting hypotheses concerning the sites of bromsulphalein removal. Data pertaining to this controversy will be submitted in subsequent papers of this series. For the moment, the role of certain obvious extrahepatic sites may be mentioned. The urine invariably contains some bromsulphalein. In normal subjects, 1-2 per cent of any amount given in a single injection is lost through the kidney during the subsequent 2 hours. In patients with hepato-biliary disease, however, the amount is considerably in-

\* Although bromsulphalein is a soluble and dialyzable substance, it appears to be bound to proteins the moment it is injected into blood. We have confirmed the findings of Robinson (10) that bromsulphalein dissolved in saline dialyzes readily through a cellophane bag, but that no dialysis occurs when bromsulphalein is dissolved in serum. As far as can be told by salting-out techniques, the greater part of bromsulphalein is bound to albumin. If one mg. of bromsulphalein is added to 2 ml. of serum diluted to 10 ml. with normal saline solution (approximate albumin content = 80 mg.), little dialysis through a cellophane bag takes place. One ml. of serum diluted to 10 (approximate albumin content = 40 mg.), however, does not prevent dialysis of the same amount of bromsulphalein.

creased, and about 5-10 per cent of the dose may appear in the urine during this time interval. For example, a patient with moderately severe hepatitis was given 300 mg.; urine collected for 2 hours thereafter contained 26.3 mg. of bromsulphalein. When the standard dose of bromsulphalein was given to 3 patients with cirrhosis and ascites, ascitic fluid collected 2-4 hours later contained no measurable quantities of the dye. In one patient with a traumatic chylothorax, the chylous effusion contained no measurable bromsulphalein 45 minutes after its injection. It would appear that loss of bromsulphalein into the urine or ascitic fluid is usually negligible, but that urinary loss must be taken into account in patients with severely damaged livers.

As stated at the outset, these studies were undertaken to obtain more information concerning the rate and character of bromsulphalein disappearance; they were not designed for the purpose of introducing further modifications of existing liver function tests. Thus our methods and results may find application in the investigation of normal and abnormal hepatic function, but for routine clinical use, the standard bromsulphalein test<sup>11</sup> is not only satisfactory but preferable. Our results, furthermore, are not necessarily applicable to laboratory animals; Stanley<sup>12</sup> was unable to establish a constant PDR in two dogs.

#### SUMMARY

The disappearance of bromsulphalein from the blood was studied after single injection of the dye in healthy subjects and in patients with and without hepatic disorders.

In most normal subjects, a constant proportion of the dye disappeared per minute. This proportion remained constant for a period of 30 minutes after injection of the dye, or, if disappearance was rapid, until the plasma contained less than 5% of the injected amount. The proportion removed was called the Percentage Disappearance Rate (PDR). Its normal range lies between 10 and 16 per cent per minute.

In some normal subjects and in patients with hepato-biliary disorders, PDR did not remain constant but decreased to a variable degree during the 30 minute period.

Many patients with cirrhosis and some with congestive failure exhibited a very low PDR, but one that remained constant for 30 minutes or longer.

Bromsulphalein was lost to a slight extent in the urine of normal subjects. In patients with hepato-biliary disease, the loss amounted to 5-10 per cent of the injected dose. No dye was found in ascitic fluid.

The results suggest that the disappearance of bromsulphalein is determined by one rather than by several consecutive mechanisms.

We acknowledge with thanks the technical assistance of Miss Doris Bullard.

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## INFECTIOUS MONONUCLEOSIS AND INFECTIOUS HEPATITIS: STUDIES BEARING ON CERTAIN RESEMBLANCES AND DIFFERENCES\*

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### INTRODUCTION

Clinical similarities between infectious hepatitis and infectious mononucleosis have long been appreciated. Jaundice, probably the most prominent symptom attracting attention to the liver, has been observed repeatedly in patients considered to have infectious mononucleosis.<sup>1-9</sup> Our interest was aroused by hematologic changes suggestive of infectious mononucleosis noted surprisingly often by one of us in soldiers with viral hepatitis<sup>10</sup>. This prompted us to investigate some of the other laboratory phenomena about which little information was available at the time. Accordingly, in April 1946 we began to make serial observations of the behavior of the heterophile antibodies in patients with infectious hepatitis whose hepatic function we were studying. Similar observations were begun at this time on patients with infectious mononucleosis. Our purpose was to learn whether these phenomena were similar and wherein they might differ in these two disorders. We hoped from such an evaluation not only to add to our knowledge, but also to obtain clues or guides which might prove useful in differential diagnosis. The present report deals with the results of this study.

### MATERIAL

Thirty-five patients with clinical features and laboratory findings consistent with infectious (viral) hepatitis comprised the group studied for changes in this disorder. Most of them were soldiers†. Some appeared to have hepatitis of the serum variety. All save one exhibited clinical jaundice at some time in their illness. Although most were in the acute phase, a few were convalescent or in the chronic phase of the disease when initially seen.

As representative of infectious mononucleosis, 12 acutely ill patients were carefully selected. In each case the clinical features were compatible with (Table 1) and the laboratory findings (Table 2) characteristic of infectious mononucleosis. Two were clinically jaundiced when first examined.

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† We are indebted to Lt. Col. Henry A. Kind and the medical officers assigned to the Gastro-Intestinal Section of Tilton General Hospital, Fort Dix, N. J., for the opportunity to study these patients.

Even though the patients available for study were few in number, they have the merit of being carefully chosen. They have the additional merit of being

TABLE 1

*Perinent Clinical Findings In Selected Group of 12 Patients Considered To Have Infectious Mononucleosis*

CASE	AGE	SEX	OROPHARYNG.	CERVICAL ADENOPATHY	HEPATOMEGL.	SPLENOMEG.	TEMP. (MAX.)	JAUNDICE
1	29	M	+4	+2	0	0	103.4	0
2	4	M	+2	+3	+4	+2	102.0	0
3	20	F	+4	+4	+2	±	101.3	+2
4	12	F	+3	+2	+3	±	103.8	+1
5	26	M	0	+1	+1	+1-+2	101.2	0
6	19	F	0	+2	0	±	102.0	0
7	19	F	+4	+3	0	±	101.0	0
8	26	F	0	+2	0	0	102.4	0
9	19	F	+2	+2	0	0	102.0	0
10	20	F	±	+1	0	0	102.0	0
11	24	F	+2	+1	0	0	101.0	0
12	20	F	+4	+4	+1	+1-+2	101.0	0

TABLE 2

*Perinent Laboratory Data In Selected Group of 12 Patients Considered to Have Infectious Mononucleosis*

CASE	TOTAL LEUK. (MAX.)	LYMPHOCYTES		HETEROPHILE ANTIBODY TITER	
		%	Atypical	Presumptive	After Absorption Boiled G.P. Kidney
1	18,400	72	+	1:896	—
2	18,000	70	+	1:224	—
3	14,950	80	+	1:224	—
4	13,400	37	+	1:224	—
5	24,750	69	+	1:448	1:112
6	13,700	91	+	1:112 (1:56)	— (1:28)
7	13,100	51	+	1:1792	1:448
8	12,250	85	+	1:1792 (1:896)	— (1:448)
9	17,800	83	+	1:448	1:224
10	11,600	78	+	1:448 (1:224)	— (1:112)
11	13,650	76	+	1:224	1:224
12	13,550	53	+	1:896	1:896

serially followed in nearly every instance, some for long periods of time. The data, while not impressively large in the aggregate, nevertheless are of sufficient size to indicate the trends in which we were interested.

## STUDIES

All patients with infectious hepatitis were serially studied from the standpoint of hepatic tests throughout the period they were under observation. The results so obtained were used for comparison with similar results in the infectious mononucleosis group. On 25 of the infectious hepatitis patients, 129 determinations of heterophile antibody titer were made over variable periods after the onset of illness. Heterophile antibody titer was also determined after absorption with boiled guinea pig kidney in 22 instances and in 9 instances after absorption with boiled beef erythrocytes as well. In addition, a few observations were made on the change in titer following incubation with human liver and after refrigeration of serum for variable periods at 4°-8° C.

Hepatic tests were serially performed on each patient with infectious mononucleosis over a period ranging from 4 to 225 days after the onset of symptoms. In all, 74 determinations of cephalin cholesterol flocculation, 73 of colloidal gold, 74 of thymol turbidity, 68 of 18 hour turbidity ratio, 34 of esterified to total serum cholesterol ratio, 29 of serum alkaline phosphatase and 13 of sulfobromophthalein excretion were made. Urine bilirubin, serum protein fractionation, oral galactose tolerance, oral and intravenous hippuric acid synthesis and Takata-Ara tests were also performed in some cases, but are not included in this report. Heterophile antibody tests were done in each case and repeated serially over a period ranging from 3 to 225 days after the onset of illness. In all, 68 titer determinations, 48 guinea pig absorption tests, and 40 beef cell absorption tests were made.

## METHODS

*Heterophile antibody agglutination and absorption tests* were determined after the method of Davidsohn<sup>11</sup> with minor modifications†. Following their final preparation the tubes were permitted to stand at room temperature for 2 hours and were then placed in the refrigerator overnight. Readings were made the following morning approximately 18 hours after final preparation. The tubes were permitted to stand at room temperature for 20 minutes after removal from the refrigerator before being read. All readings were macroscopic and only tubes showing unequivocal agglutination were accepted as positive; ± readings were considered negative. The sheep cells varied in age, but were always more than 1 and never more than 7 days old.

The *hepatic tests* employed in the study of these cases are shown in Table 3.

† These tests were all performed in the Serological Division of the Department of Bacteriology and Immunology of Temple University School of Medicine by Mrs. Elsa R. Lynch.

## RESULTS

*Heterophile Antibody in Infectious Hepatitis*

The highest heterophile antibody titer recorded was 1:56 (Table 4). A titer of this magnitude was exhibited by only 3 of the 25 patients (12 per cent)

TABLE 3  
*Hepatic Tests Employed*

NOTE: Some of these were performed in the hospital laboratory during initial hospitalization which explains the variation in methods as regards certain tests.

TEST	METHOD	ABNORMAL
(a) Total Serum Bilirubin	(a) Malloy and Evelyn (35) (b) Thannhauser and Anderson (36) (8 instances)	>1.0 mg./100 ml.
(b) Prompt Direct-Reacting Serum Bilirubin	Malloy and Evelyn (35) using 1 minute reading of Ducci and Watson (37)	>0.2 mg./100 ml.
(c) Cephalin Cholesterol Flocculation	Hanger (38)	> $\pm$ 24 hour reading (5 instances) >1 + 48 hour reading
(d) Colloidal Gold	MacLagan (39) modified to read from 0 to 4+	>1+
(e) Thymol turbidity	(a) Shank and Hoagland (40) modification of MacLagan (41) (b) MacLagan (41) employing Kingsbury-Clarke protein standards (11 instances)	3 units or >
(f) 18 hour Turbidity Ratio	Shay, Berk and Siplet (12)	<85%
(g) Thymol Flocculation	Neefe (42)	>1+
(h) Total and Esterified Serum Cholesterol	Bloor and Knudson (43)	Ester: Total Ratio <50%.
(i) Serum Alkaline Phosphatase	(a) Shinowara, Jones and Reinhart (44) (b) Bodansky (45) (4 instances)	>9 units
(j) Sulfobromophthalein Excretion	(a) Rosenthal & White (46) modified for use with Evelyn photoelectric colorimeter (2 mg./kilo.) (b) Same using comparator block (2 instances) (c) Same using comparator block and 5 mg./kilo (1 instance)	>4 units >5% at 30 min. >0 at 30 min. >0 at 45 min.

and occurred only 3 times in the 129 determinations (2.3 per cent). All three 1:56 readings were encountered late in the course of the disease (131, 135 and approximately 241 days after the onset of illness). In one patient this reading represented the sole determination made. In the remaining 2 patients, however, one had 2 and the other 13 previous readings all of lesser degree. Un-

fortunately, absorption tests were not made on any of the sera showing a titer of 1:56.

The highest unabsorbed titer of those sera on which absorption tests were done was 1:28. In every instance absorption was apparently complete with both boiled guinea pig kidney (22 tests) and boiled beef erythrocytes (9 tests) (Table 4). Absorption tests on 8 sera using human liver yielded inconsistent results.

TABLE 4  
*Heterophile Antibody In Infectious (Viral) Hepatitis (25 Cases)*

DURATION OF DISEASE <i>weeks</i>	NO. CASES	PRESUMPTIVE TEST		ABSORPTION TESTS			
		No. Tests	Titer Range	Boiled Guinea Pig Kidney		Boiled Beef Erythrocytes	
				No. Tests	Titer <1:7	No. Tests	Titer <1:7
1	5	5	<1:7-1:28	2	2	1	1
2	6	6	1:7-1:14	5	5	2	2
3	12	12	<1:7-1:28	3	3	2	2
4	10	10	<1:7-1:28	4	4	1	1
5	10	10	<1:7-1:28	—	—	—	—
6	12	12	<1:7-1:28	1	1	—	—
7	10	10	<1:7-1:28	1	1	1	1
8	10	10	<1:7-1:28	1	1	—	—
9-12	9	23	<1:7-1:28	1	1	—	—
13-16	7	13	<1:7-1:28	—	—	—	—
17-20	3	6	<1:7-1:56	1	1	—	—
21 and over	5	12	<1:7-1:56	2	2	2	2

### Flocculation Tests

The flocculation tests (cephalin cholesterol, colloidal gold, thymol turbidity and 18 hour turbidity ratio) showed a striking tendency to be positive in the early stages of infectious mononucleosis (Figures 1 and 2). In every one of our 12 cases at least one of the tests was positive on initial examination (4 to 16 days after onset). All 4 tests were positive in 8 cases, 3 tests were positive in 2 cases, 2 tests were positive in 1 case, and only the thymol turbidity was positive in the remaining case.

Striking also was the tendency for these tests to remain positive for surprisingly long periods of time (Figures 1 and 2). Three patients exhibited normal values for the flocculation tests 47, 52, and 69 days respectively after onset. Five patients still showed abnormal reactions when last examined, but were lost to further observation. One of this group had been followed up to 75 days after the beginning of disease. Of the remaining 4 patients, only the cephalin cholesterol test was done 46 days after onset in 1 and this was ab-

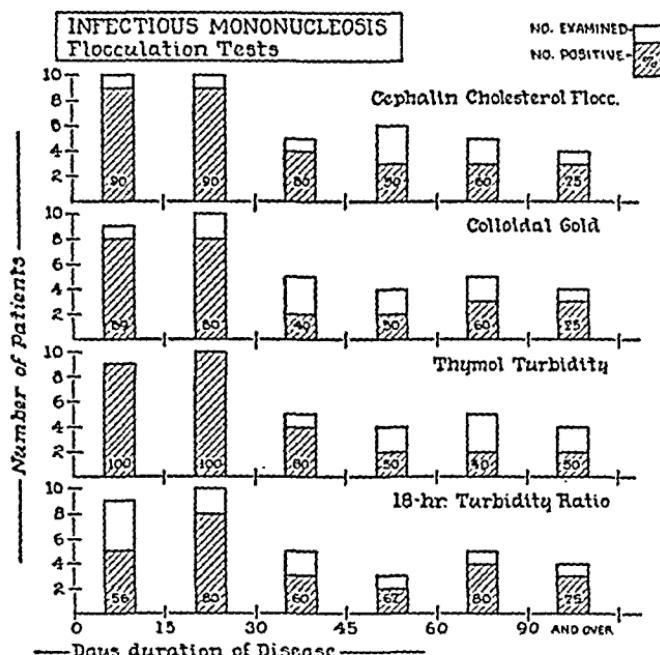


FIG. 1. Flocculation Tests: Comparison of the total number of patients with infectious mononucleosis examined during various intervals after onset of disease with the number showing positive tests.

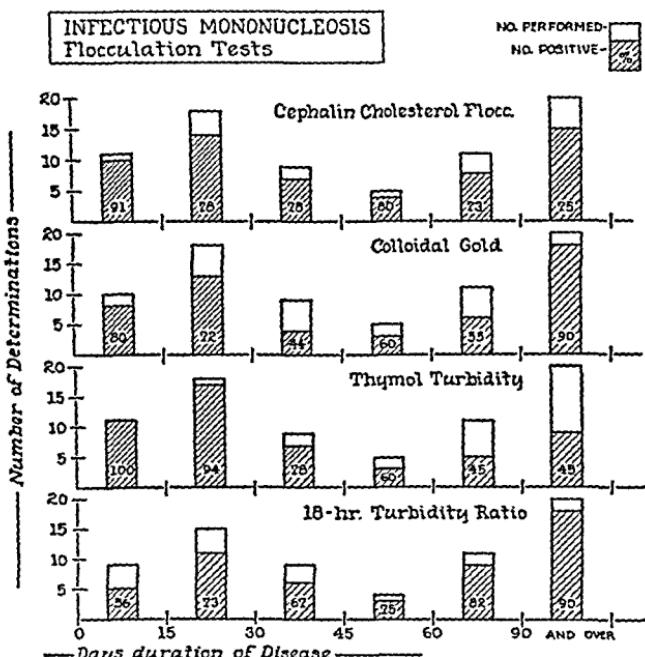


FIG. 2. Flocculation Tests: Comparison of the total number of tests in patients with infectious mononucleosis with the number positive during various intervals after onset.

normal. The other 3 showed abnormal readings for all tests except the thymol turbidity when last examined 225, 147, and 125 days respectively after onset.

This tendency for the flocculation tests to be abnormal early and to remain so for a long time parallels, in general, our experience in infectious hepatitis<sup>12</sup>. The trends on the part of the individual tests, however, cannot be accurately compared because the mononucleosis cases available for study during the later stages of disease were especially few. Nevertheless, it may be noted that, in comparison to infectious hepatitis, the thymol turbidity test in infectious mononucleosis tended to be even more often positive than the 18 hour turbidity ratio during the very early stages. In the late stages, the thymol turbidity not only

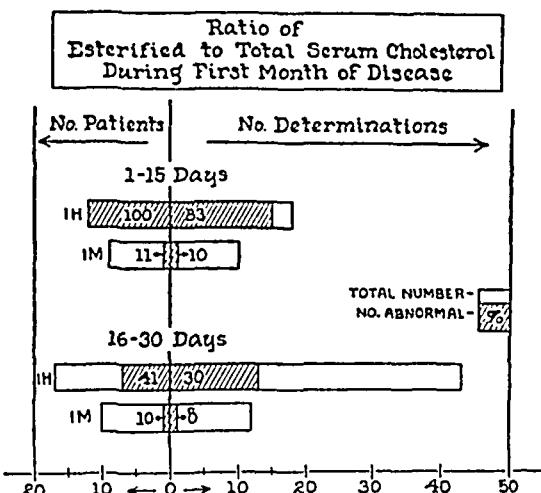


FIG. 3. Ratio of Esterified to Total Serum Cholesterol: Comparison of the total number of patients (left) and the total number of determinations (right) with the number abnormal during the first month of disease. Infectious Hepatitis (IH). Infectious Mononucleosis (IM).

reversed its relationship with the 18 hour turbidity ratio, but also tended to return to normal earlier than the other flocculation tests.

#### *Ratio of Esterified to Total Serum Cholesterol*

An abnormal ratio of esterified to total serum cholesterol was observed in our mononucleosis cases only during the first month after onset. The number of patients exhibiting an abnormal ratio and the number of determinations which were abnormal were both remarkably few (Figure 3). These findings are in sharp contrast to those in infectious hepatitis as shown in Figure 3. The number of cases and the average number of determinations per patient are obviously not identical in these two groups. Nevertheless, comparison between them appears to be entirely valid. In both diseases, the per cent of abnormal values computed from the results obtained in the first samples examined on each case during the intervals indicated, did not differ significantly

from the per cent of abnormal values computed from the total samples examined during these same intervals. This indicates that the latter values are representative and may be compared. In both the 1-15 and 16-30 day intervals, the difference in per cent of abnormal values in infectious mononucleosis as compared with infectious hepatitis proved to be statistically significant. §

#### *Sulfobromophthalein Excretion in Infectious Mononucleosis*

Sulfobromophthalein excretion was very slightly affected in the 7 cases of infectious mononucleosis we were able to examine. Only 2 of 13 tests were

TABLE 5  
*Sulfobromophthalein Excretion Test In Infectious Mononucleosis*

CASE	DURATION OF DISEASE	% SULFOBROMOPHTHALEIN RETAINED*
1	days	
	35	5.5
2	47	4.8
	18	0.0**
8	58	0.0**
	197	6.6
9	29	2.2
10	24	4.8
	31	2.6
	91	3.1
11	83	4.1
	125	2.2
12	6	3.0
	46	0.0***

\* Except as otherwise noted represents photocolorimetric determination of per cent of dye remaining in serum 30 minutes after injection of 2 mg. of sulfobromophthalein per kg. body weight.

\*\* Comparator block reading—2 mg./kg.—30 min.

\*\*\* Comparator block reading—5 mg./kg.—45 min.

abnormal (Table 5). Moreover, the maximum retention in any case was 6.6 per cent and the serum in this instance was slightly hemolyzed. Normal readings were obtained at varying periods during the first month of disease and, of the 11 normal results, 10 were obtained at times when one or more of the flocculation tests was abnormal.

#### *Serum Alkaline Phosphatase*

As was the case with esterified to total cholesterol ratio, elevation of serum alkaline phosphatase was found only during the first month of illness in the mononucleosis cases. The incidence of elevated values, both in terms of

§ The test for significance employed was the calculation of chi square in a 2 x 2 table under the hypothesis of independence.

patients as well as determinations, coincided closely with that in infectious hepatitis (Figure 4). Analysis indicated that these groups were statistically

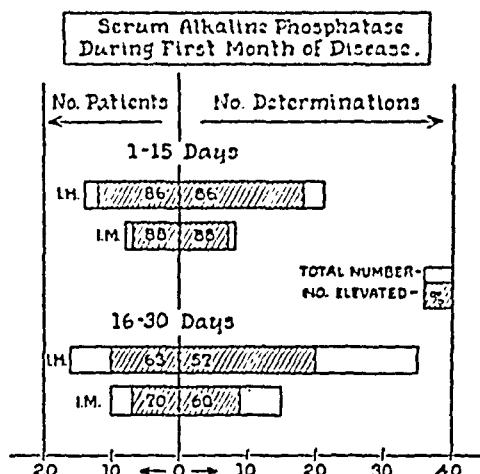


FIG. 4. Serum Alkaline Phosphatase: Comparison of the total number of patients (left) and the total number of determinations (right) with the number elevated during the first month of disease. Infectious Hepatitis (IH). Infectious Mononucleosis (IM).

TABLE 6

*Serum Alkaline Phosphatase in Non-Jaundiced Patients With Infectious Mononucleosis*

DURATION OF DISEASE	PATIENTS		DETERMINATIONS		>20 U (S-J-R) OR > 10 U (B)	
	No.	% With Elev.	No.	% With Elev.	No.	% of Tot. Det'n.
days 1-30	11	64	19	63	3	16

TABLE 7

*Comparative Values for Simultaneously Determined Bilirubin, Total Cholesterol and Alkaline Phosphatase in 3 Serum Samples Obtained From 2 Non-Jaundiced Patients With Infectious Mononucleosis Who Exhibited Marked Hyperphosphatasemia*

SERUM ALKALINE PHOSPHATASE*	SERUM BILIRUBIN (MG. %)		SERUM TOTAL CHOLESTEROL mg. %
	1 Min.	Total	
33.3	—	0.70	222
28.3	—	0.61	246
45.0	0.21	0.55	183

\* Shinowara-Jones-Reinhart Units.

comparable and the chi square test confirmed a lack of significant difference between them. It must be emphasized, however, that nearly all the mononucleosis cases were never jaundiced, whereas all of the hepatitis cases were

jaundiced or recovering from jaundice during the periods considered. The high incidence of increased phosphatase activity in mononucleosis cases without jaundice is quite apparent when only those observations made in cases without jaundice are considered. As shown in Table 6, two-thirds of such cases showed increased phosphatase activity during the first month of disease. In 2 of these cases the degree of activity was pronounced and no cause was apparent. As shown in Table 7, serum bilirubin and total cholesterol values determined at the same time were within normal limits.

#### DISCUSSION

A heterogenetic antibody which agglutinated sheep erythrocytes was found by Eaton and his co-workers<sup>13</sup> in certain cases of acute infectious hepatitis. Assembling their data without selection as to date of onset, and recording the titers as the original dilution of serum, they found titers of 1:160 or greater in 8 per cent of 154 cases of postvaccinal hepatitis and 13 per cent of 68 cases of infective hepatitis. A titer of 1:360, however, was very rare and the titers in general were lower than those in infectious mononucleosis<sup>14</sup>. In contrast, none of our 25 patients exhibited unabsorbed titers in excess of 1:56 as expressed in terms of final dilution of serum. Similarly, none of 37 patients with hepatitis developing after mumps convalescent plasma studied by Hawley and his associates<sup>15</sup> showed a heterophile antibody titer greater than 1:14. deVries<sup>16</sup>, Barker, Capps and Allen<sup>17</sup> and Dempster<sup>7</sup> made mention that heterophile antibodies are absent or negative in hepatitis but gave no data. Cohn and Lidman<sup>18</sup> also stated that heterophile agglutination in their patients with infectious hepatitis yielded titers of 1:14 or less but gave no further details. Havens, Gambescia and Knowlton<sup>19</sup> have just completed a study of the heterophile agglutination in 508 soldiers with viral hepatitis. They found that only 16 or 3 per cent developed titers of 1:56 which were reduced to 1:7 or negative by absorption on boiled guinea pig kidney. It appears, then, that a significant rise in sheep cell agglutinins must occur but rarely in infectious hepatitis.

Though a high heterophile antibody titer may be taken as evidence favoring mononucleosis over hepatitis, it is incorrect to assume that a low titer establishes hepatitis over mononucleosis. The maximum heterophile antibody titer in infectious mononucleosis may be delayed in its development<sup>8, 9, 21</sup>. Hence, serial studies over a period of weeks is essential before concluding that sheep cell agglutinins are not increased. Even so, there still remains a not insignificant number of patients with what appears clinically to be mononucleosis who are sero-negative. The percentage of cases with negative agglutination tests has been reported to vary in different series from 0 to 57<sup>21</sup>. Even

with the use of confirmatory absorption studies, Dempster<sup>7</sup> found 26 per cent of his cases to be definitely sero-negative.

To help overcome some of these uncertainties, Davidsohn<sup>11</sup> and, more recently, Barrett<sup>21</sup> have advocated the use of absorption tests. These have as their premise the demonstration that the antibody in mononucleosis is slightly or not at all absorbed by beef erythrocytes. Clinical experience with these tests has shown them to be of definite value, especially in cases with borderline titers and in cases complicated by serum injections<sup>7, 22</sup>. However, they have not proved to be uniformly satisfactory, particularly in cases with low titers<sup>8, 21, 22</sup>. Six of our 12 cases of infectious mononucleosis were serially followed until the agglutinin titer had become 1:56 or less. In 4 cases, guinea pig kidney absorption was apparently complete, while in 1 case beef cell absorption was incomplete in serum samples exhibiting these low titers. Despite these inconsistencies, it is of interest that the agglutinins in our cases of infectious hepatitis were uniformly completely absorbed by both guinea pig kidney and beef erythrocytes. The human liver absorption test of Eaton et al<sup>13</sup> may perhaps prove useful in distinguishing low titer cases of hepatitis from mononucleosis. Our experience with only 8 tests, however, was disappointing.

The high degree of positivity of the flocculation tests in infectious mononucleosis is notable. Our observations in this respect are in accord with those of others<sup>8, 9, 18, 23, 24, 25, 26, 27</sup>. The tendency for positive tests to persist is also impressive. The duration of positive flocculation tests in our cases appears to be even longer than in other groups similarly studied<sup>18, 24, 26</sup>. Especially noteworthy is the persistence of positive tests in 2 of our patients on whom serial observations were obtained up to 12 and almost 5 months respectively after onset. Both are young females who, despite the abnormal flocculation reactions, appear well and able to carry on their usual work. We were impressed by the tendency for thymol turbidity to revert to normal before the other flocculation tests. Evans<sup>27</sup> also commented that abnormal thymol turbidity tests were more transient than abnormal cephalin cholesterol flocculation tests. On the other hand, Brown, Sims and Clifford<sup>26</sup> found that the average period from onset to the last abnormal reading was a few days shorter for cephalin cholesterol than for thymol turbidity.

The fact that tests accepted as measures of liver function were only infrequently abnormal in mononucleosis is of great interest. Particularly so, since they yielded normal results even when performed during the first month of disease and at times when the flocculation reactions were abnormal. Our experience, however, is admittedly limited and the findings of other investigators have not been uniform. Thus Cohn and Lidman<sup>18</sup> found an abnormal cholesterol ester ratio in only 1 of 5 cases, but an abnormal sulfobromophthalein

test at some time in all of their 15 cases. DeMarsh and Alt<sup>24</sup> Pollock<sup>5</sup> and Wechsler et al<sup>8</sup> also reported a high incidence of abnormal sulfobromophthalein tests in their cases. It is not clear, however, whether the patients studied by Pollock and by Wechsler and his group were jaundiced at the time the tests were done.

This contrast between the flocculation reactions on the one hand and accepted liver function tests on the other, raises a question regarding the significance of the former. The weight of evidence suggests that the flocculation phenomena depend essentially on alterations in serum proteins, and in the case of the thymol reaction at least, on serum lipids as well<sup>12, 28, 29</sup>. Infectious mononucleosis notoriously affects reticuloendothelial and lymphatic structures throughout the body. These structures are known to be intimately concerned with the formation and storage of serum globulin<sup>30</sup>. The appearance of atypical lymphocytes in the blood and immunologic phenomena represented by an increase in heterophile antibodies are well recognized features of mononucleosis. Though Brown and his associates<sup>26</sup> found no significant correlation between the heterophile antibody reaction and the cephalin cholesterol and thymol tests, there was a rough parallelism in the progressive decline in these reactions in our cases. Electrophoretic analyses of the serum proteins in mononucleosis have revealed increases in beta and gamma globulin<sup>18, 27</sup>. In the liver, the outstanding morphologic alteration in mononucleosis is lymphocytic cellular infiltration, most pronounced in the peri-portal areas. Kupffer cell hyperplasia is also prominent. These considerations suggest that in mononucleosis, even more clearly than in hepatitis or other diseases in which the liver is involved, the flocculation phenomena are associated primarily with alterations in protein and perhaps lipid components of the serum. They would appear to be related to the liver changes which occur only insofar as the latter contribute to these alterations.

The similarity in overall incidence of hyperphosphatasemia in infectious hepatitis and infectious mononucleosis during the first month of disease, ignores the important fact that all of the cases of hepatitis were jaundiced whereas those of mononucleosis were nearly all free of jaundice. In view of this important difference it is quite possible that the mechanisms responsible for the elevation in serum alkaline phosphatase are not identical in these disorders.

A noteworthy feature of the serum alkaline phosphatase behavior in non-jaundiced patients with infectious mononucleosis, was the occasional occurrence of pronounced elevations without obvious cause. The normal values for simultaneously determined bilirubin concentration and total cholesterol in those sera showing marked elevations of alkaline phosphatase lend no support to biliary obstruction as the cause. On the other hand, they do not exclude this possibility with absolute certainty. Discrepancies of this charac-

ter in known cases of biliary obstruction have been repeatedly observed<sup>31, 32, 33</sup>. The cellular aggregates in the periportal areas as well as possible enlargement of lymph nodes in the liver hilum could conceivably exert sufficient pressure on the biliary tree to bring about elevation of serum phosphatase. White blood cells are known to contain alkaline phosphatase and Woodard and Craver<sup>31</sup> have noted increased phosphatase activity in the lymphomatoid diseases. It would not seem likely, however, that phosphatase activity of the degree observed in mononucleosis can be accounted for from this source.

#### SUMMARY AND CONCLUSIONS

Serial study of heterophile antibody behavior, the flocculation tests, and certain hepatic function tests in cases of infectious hepatitis and infectious mononucleosis indicated the following resemblances and differences:

(1) Significant increases in heterophile antibody titer occur only rarely in infectious hepatitis in contradistinction to infectious mononucleosis.

(2) The agglutinin in the serum of cases of infectious hepatitis differs from that in infectious mononucleosis in its absorbability by guinea pig kidney.

(3) In both infectious hepatitis and infectious mononucleosis the serum flocculation tests (cephalin cholesterol, colloidal gold, thymol turbidity and 18 hour turbidity ratio) show a marked tendency to be positive early and to remain positive for long periods.

(4) Liver function measured by the ratio of esterified to total cholesterol is far less often abnormal in infectious mononucleosis than in infectious hepatitis. Sulfobromophthalein excretion is also only occasionally abnormal in infectious mononucleosis.

(5) It is suggested that in infectious mononucleosis, even more clearly than in infectious hepatitis, the flocculation phenomena are associated primarily with alterations in the serum proteins and perhaps lipids. They would appear to be related to the liver changes in the disease only insofar as the latter contribute to the alterations in the protein and lipid components of the serum.

(6) Serum alkaline phosphatase shows increased activity in most cases of both infectious mononucleosis and infectious hepatitis during the first month of disease. However, since most of the mononucleosis cases were not jaundiced while all of the hepatitis cases were jaundiced, the mechanisms responsible for hyperphosphatasemia may not be identical in these disorders. The degree of elevation of serum alkaline phosphatase in non-jaundiced patients with infectious mononucleosis may occasionally be pronounced.

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## FACTORS AFFECTING PROTEIN BALANCE IN THE PRESENCE OF CHRONIC VIRAL LIVER DAMAGE\*

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### INTRODUCTION

For the purposes of this presentation, chronic hepatitis will be considered as the sequella of acute hepatitis. Under the head of chronic (viral) hepatitis will arbitrarily be classified all patients who have had clinical, chemical, and histological evidence of active liver damage for more than six months, following a known or presumptive attack of acute viral hepatitis.

Since, in the experience of all students of acute viral hepatitis, the disease tends to be self-limiting in the vast majority of cases, one is immediately faced with the question as to why a very small group of patients fails to make an adequate recovery under conditions of bed rest, high protein, high vitamin intake. The answer to this question revolves around the matter of a continuing viral infection on the one hand, and the possibility of some basic metabolic defect on the other. We believe that the data here presented would indicate that both of these factors are present; but that the question of which is in a primary role is still to be answered.

### OBSERVATIONS

Out of several score of acute hepatitis patients who have been studied intensively by this group, only three have fulfilled the requirements for the diagnosis of chronic hepatitis. This paper will concern itself with certain observations dealing with protein metabolism which have been obtained on two of these men.

Patient C. C., a man of 25 years, had a rapidly progressing jaundice in August 1946, while aboard ship in the South Pacific. His past history was negative except for mild jaundice about 10 years previously. He was first admitted to our ward in December 1946, at which time he was still clinically jaundiced, had multiple spider angiomata, an enlarged tender liver and some weakness and anorexia. No evidence

\* This work has been performed under a contract between the Office of Naval Research and the University of California.

The data here presented are derived from the joint efforts of the group who have been, or who are affiliated with the Metabolic Research Unit, notably, Drs. H. C. Barton, H. A. Harper, W. E. Larsen, S. Morgen, D. P. McCallie, G. D. Michaels, J. S. Shaver, and H. A. Weiss; a group of loyal and able technical assistants, notably, C. T. Anderson, E. K. Flanagan, J. McB. Frantz, J. R. Hess, M. E. Hutchin, M. F. Jack, E. E. Mecum; and four Navy Hospital Corpsmen—J. S. Czech, R. A. Springer, V. T. Thompson, and A. E. White.

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of parasitic infestation was found. All usual liver function tests were abnormal, i.e., cephalin flocculation, bromsulphalein, thymol turbidity, serum bilirubin, and hepatic glycogen storage. Two months later, at which time liver biopsy was performed (Fig. 1), he was unchanged except for loss of his clinical jaundice. In the months which followed, he was given the benefit of all usual therapeutic agents, including large dosage of methionine and choline under balance study conditions. Inasmuch as we had demonstrated significant nitrogen retention, coupled with clinical improvement, in some of our "cirrhosis" patients when these agents were added to a high protein, high vitamin intake (Fig. 2), we were unhappily surprised to find no such effect in this man with chronic viral hepatitis—instead there was actually a decrease in the positiveness of the nitrogen balance induced by a diet in which the major



FIG. 1. Liver biopsy (x 70) in patient C. C., six months after the clinical onset of acute hepatitis, showing evidence of continued round cell infiltration.

portion of the protein was derived from 150 grams of protein hydrolysate intravenously, daily (Fig. 3)\*.

In September 1947, at which time his clinical and chemical status was little changed, another liver biopsy was obtained. An active inflammatory process was still present (Fig. 4). In February 1948, evidence of continuing hepatitis still being present, he was again placed on a balance regime, and was found to be in negative nitrogen balance. When testosterone\*\* was administered, he went into positive balance, and so remained until the steroid was discontinued, at which time he reverted to negative balance (Fig. 5). During this period of testosterone administration, he showed some clinical and chemical evidence of improvement. It is still too soon to emphasize this unduly except to note that *no* other agent had produced any evidence of benefit whatsoever.

\* The hydrolysate (Amigen) was generously supplied by Dr. Warren Cox of the Mead-Johnson Company.

\*\* The steroids used in this study were supplied through the courtesy of Dr. Edward Henderson of the Schering Corporation.

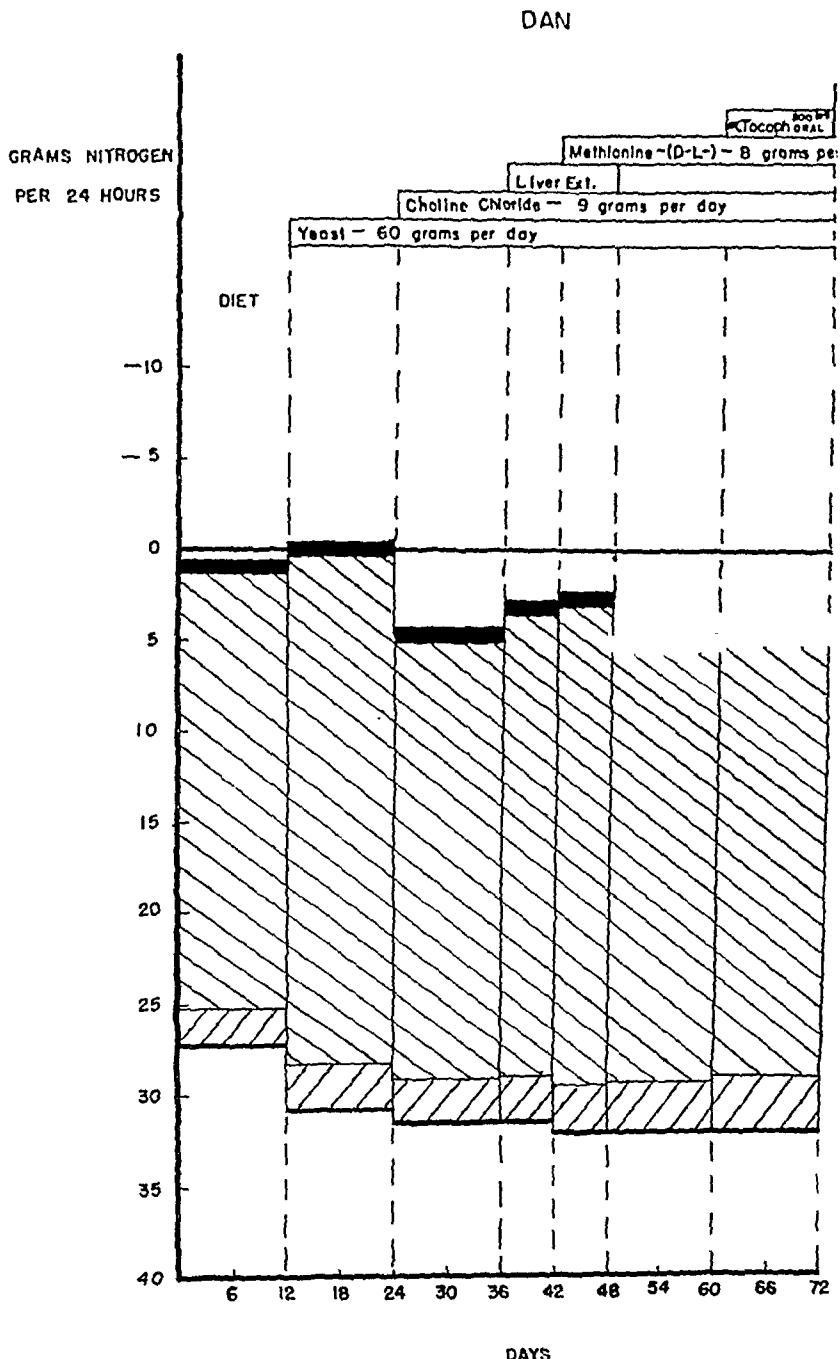


FIG. 2. Nitrogen balance study in cirrhotic A. D., showing major anabolic effects of "lipotropic" agents, over and above a high protein diet. This man had lost all histologic evidence of fatty infiltration at the time this study was carried out.

Patient R. R., a young male of 21 years, had had a history of moderately severe diarrhea and moderate abdominal distress for a period of some two months before his admission to the metabolic ward. Because of previous residence in the tropics

he was put through a rigorous search for intestinal parasites, with completely negative results.

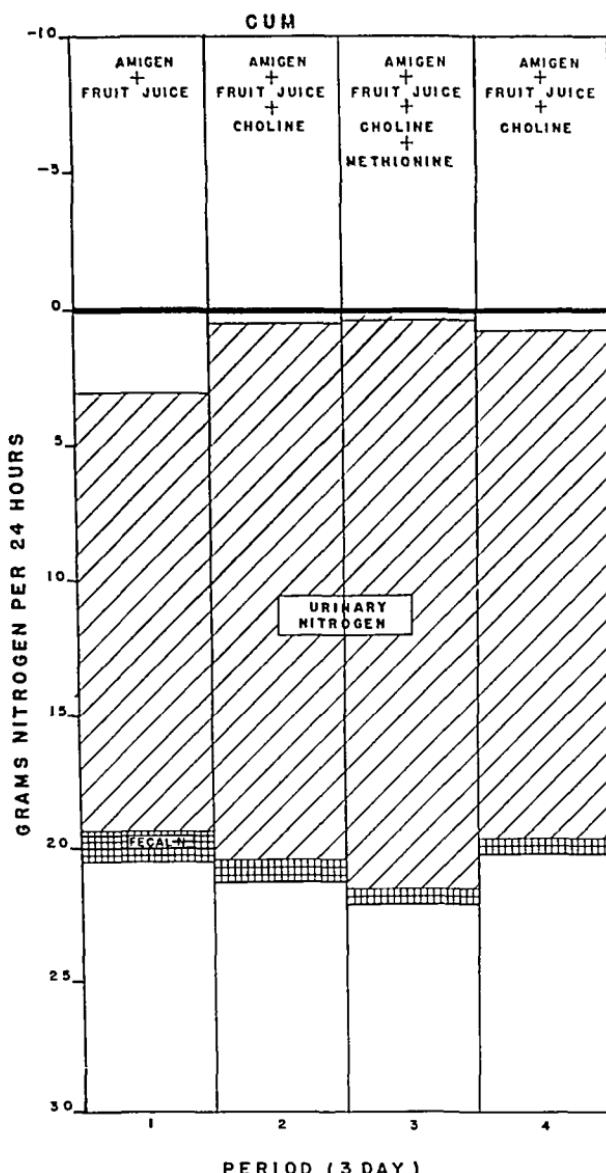


FIG. 3. Nitrogen balance study in patient C. C. Nitrogen retention is decreased rather than increased as compared to cirrhotic patient A. D., during choline and methionine administration.

On admission, he was found to have a large liver, palpable several centimeters below the rib margin, and a moderately enlarged, slightly tender spleen. He had a pronounced hepatic fetor, multiple spider angiomas, slight abnormality of the

mucous membranes, suggestion of "B deficiency", and evidence of some weight loss. No history of hepatitis or of previous jaundice was obtained. The "routine" liver function panel was abnormal throughout, as in the first patient. Liver biopsy was



FIG. 4. Liver biopsy ( $\times 100$ ) in patient C. C. obtained more than a year after the onset of his disease. Note circumscribed areas of *round cell* infiltration.

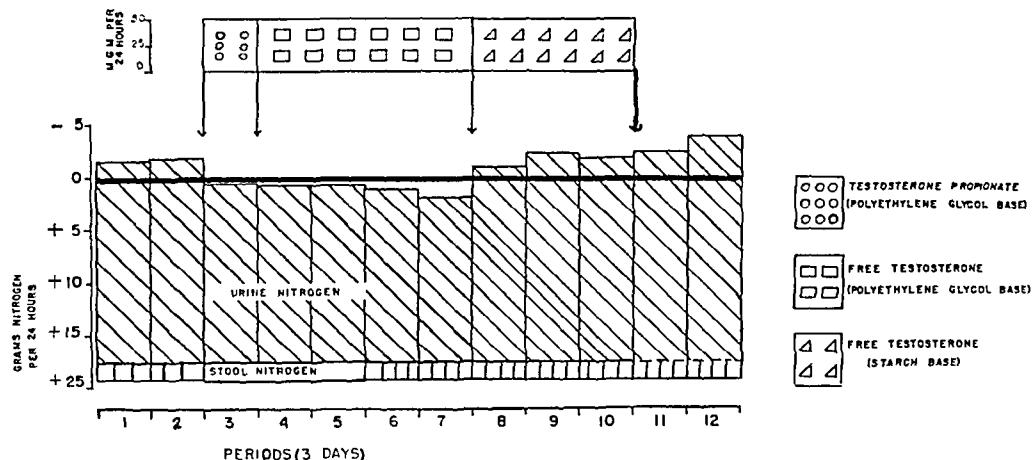


FIG. 5. Effect of anabolic steroids upon the protein balance in patient C. C. This study was done about  $1\frac{1}{2}$  years after the original attack of hepatitis. The testosterone preparations in periods 3 to 7, inclusive, were in a polyethylene glycol base and were absorbed from the buccal cavity. The steroids in periods 8, 9, and 10 were in a sugar-starch base and were apparently devoid of activity when administered buccally.

compatible with an interpretation of continuing viral infection and considerable hepatocellular damage Fig. (6).

Over a period of six months this man also received all the usual therapeutic agents, with no significant change in his clinical or laboratory status. Later, in the course of performing "methionine tolerance tests" (described elsewhere), it was noted that his urinary sulfate excretion was greatly in excess of normal (Fig. 7), and that during

a period of testosterone administration (used initially for purposes of evaluation of steroid metabolism in the presence of liver damage), the urinary sulfate fell to normal. It should be noted here that his pre-treatment 17 ketosteroid excretion (an index of



FIG. 6. Liver biopsy (x 70) on patient R. R. obtained after six months of observation. Round cell infiltration, and hepatocellular abnormality are apparent.

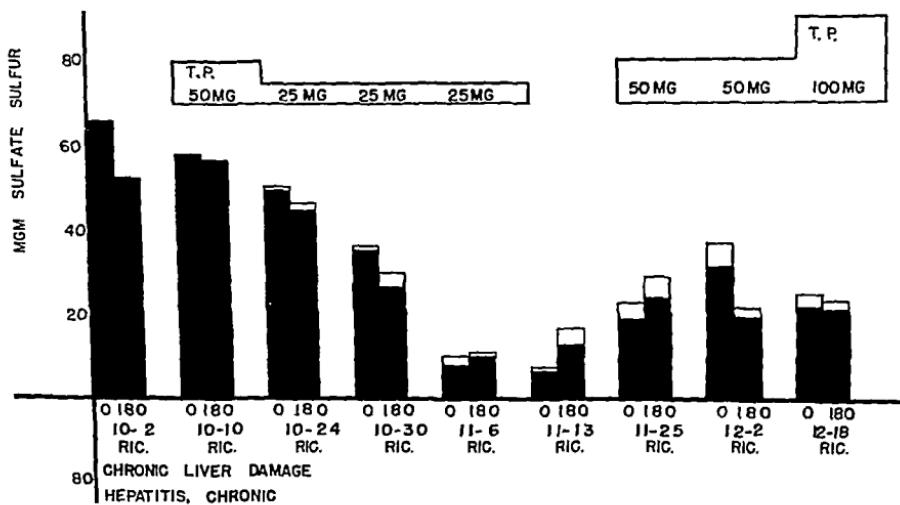


FIG. 7. Urinary sulfate excretion in patient R. R., preceding, during, and following testosterone administration. The pretreatment fasting urinary sulfate is increased approximately three times the normal amount.

endogenous production of anabolic steroids), was significantly low. During this same period (6 weeks) this man lost his hepatic fetor, had a progressive decrease in the size of his liver (eventually to the point of being non-palpable), a decrease in the number of spider angioma, and an increase in strength and well being to such a degree as to make it impossible to keep him on an inactive regime. His liver function tests improved but

are still not all within normal limits. As this is written he has been permitted to leave the hospital on a regime which includes small dosage of testosterone, high protein, high vitamin diet, and moderate activity.

#### DISCUSSION

It is not the intent of the authors to present in this paper a detailed description of metabolic studies in patients with liver disease; such studies are described elsewhere<sup>1</sup>. It is rather our intent to present the results of certain clinical, histological, and chemical observations in patients with a form of viral hepatitis which fails to follow the usual rules. These observations do assuredly *not* establish the etiology of the disease, except to indicate the *likelihood* of a continuing low grade infectious process, and the *certainty* of certain major derangements of protein metabolism. They indicate that some individuals with this disease are in negative protein balance, and that significantly increased catabolism of sulfur-containing amino acids may occur. They indicate equally that such metabolic disturbances may be corrected by the administration of protein anabolic steroids, and that the chemical improvement which results may be accompanied with rather striking clinical improvement. In view of the large volume of data in the literature, well summarized in a recent paper of Lloyd and Williams<sup>2</sup>, suggesting decreased production of at least some anabolic steroids in the presence of liver damage, and of our own findings indicating decreased 17-ketosteroid excretion in such patients<sup>1</sup>, there may be sound theoretical reasons for administering such agents. It may be well to mention here that *methyl* testosterone in our hands and in the hands of other investigators has apparently resulted in jaundice in some instances. To the best of our knowledge this has not occurred with free testosterone or testosterone propionate. Since the administration of methyl testosterone results in profound creatine formation and excretion<sup>3</sup>, it may well be that this process occurs at the expense of choline, with resultant decrease in phospholipid formation. This theory is being tested. In any event, since potent non-methylated testosterones are available, the use of methyl testosterone should be considered as being contraindicated in patients with liver disease until further knowledge is available.

#### SUMMARY

A small group of patients, who have had proven or presumptive acute hepatitis, continues to have clinical, chemical and histological evidence of active liver damage six and more months after the onset of the disease despite usually adequate "therapy". Such patients have findings suggestive of continuing viral infection, and conclusive evidence of derangements in protein metabolism in general and of excessive catabolism of sulfur-containing amino acids in

particular. These abnormalities of protein metabolism are corrected by the administration of certain protein anabolic steroids; such chemical improvement appears to coincide with significant clinical improvement.

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## CLINICAL ASPECTS OF THE SEQUELAE OF ACUTE HEPATITIS

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Ample objective evidence is now available to indicate that acute viral hepatitis is not infrequently followed by various types of sequelae<sup>1, 2, 3, 4, 5</sup>. However, due to current preoccupation with laboratory methods the clinical aspects of this subject have been relatively neglected. This is unfortunate since laboratory methods applicable to the study of liver disease are not sufficiently advanced to provide a satisfactory picture of the disease in many cases. Thus it is often difficult or impossible to correlate symptoms with liver function tests simply because we do not understand the physiologic basis for many symptoms and consequently are unable to measure the appropriate functions. For example, a patient may have laboratory evidence of residual liver disease and yet his symptoms may be due to a psychoneurosis or may be on some other unrelated basis or on the other hand, he may have typical hepatic symptoms and physical findings but only minimal or equivocal laboratory evidence of liver dysfunction. Correlation of symptoms with histopathological findings is likewise often poor. This dilemma, we believe, is best solved at present by a consideration of the clinical picture.

During the course of our studies of the convalescent stage of acute viral hepatitis in the last war<sup>1, 6, 7</sup> it became clear that a close correlation existed between the type and severity of symptoms, the presence or absence of liver tenderness, and the response of symptoms and liver tenderness to exercise. This correlation was subsequently found to hold good in the late sequelae of the disease, although the response to exertion is more difficult to demonstrate. On this clinical basis cases can be readily classified into two large groups which we have arbitrarily termed inactive and active hepatitis respectively (table No. 1). Roughly, the former represent cases with laboratory evidence of liver damage but without significant symptoms whereas the latter group includes those cases with relatively severe symptoms but either with or without corresponding laboratory evidence of liver dysfunction. Thus, these clinical correlations provide an objective method for determining whether or not symptoms are related to liver disease and have therapeutic and prognostic implications as well but do not indicate either the severity or nature of the underlying pathologic changes. Laboratory data providing this information is naturally essential.

### INACTIVE HEPATITIS

Inactive hepatitis, representing by far the largest group, includes those patients with objective evidence of liver abnormality but without significant

symptoms, liver tenderness or aggravation from exercise. Since laboratory or histologic evidence of liver disease is essential to the diagnosis, the incidence will depend upon the sensitivity of the methods employed as well as the values accepted as normal.

Extensive data is not available concerning incidence although such studies as have been made indicate that persistent bilirubinemia of the indirect type which is one of the more common residuals, occurs in about 25% of cases<sup>8</sup>. Soffer and Paulson<sup>9</sup> found the bilirubin excretion test positive in 9 of 11 late cases and Kornberg<sup>10</sup> found it positive in 10 of 16 cases. Studies on veterans under way at the present time should provide a more definitive answer.

In our experience the symptoms in this group are usually limited to fat intolerance, mild fatigue and occasionally slight right upper quadrant discomfort, but are more often entirely absent. The liver may or may not be enlarged but is characteristically not tender. Exercise does not aggravate the symptoms, produce liver tenderness nor alter the laboratory findings except

TABLE 1  
*Clinical Classification of Viral Hepatitis Residuals*

	ACTIVE	INACTIVE
Symptoms .....	Often severe	Mild and few
Liver Tenderness.....	+	0
Reaction to Exercise.....	+	0
Tendency to Relapse.....	+	0
Frequency.....	{ 10% at 4 months 3% at 1 year	?

occasionally in the case of the indirect type of serum bilirubin. Here we have noted that the bilirubinemia may increase for a period of days following strenuous exertion.

Clinically, this condition appears to be relatively static, is not ordinarily associated with relapse and the prognosis is usually good unless the patient is subsequently exposed to severe liver trauma in which case a lowered functional reserve may result in liver failure. In some cases, of course, especially where bromsulphalein retention is marked, the degree of liver damage is severe and the prognosis may ultimately be poor. Such cases are likely to have marked fatigue and severe weight loss.

#### CHRONIC ACTIVE HEPATITIS

In contrast to the inactive cases, the diagnosis of chronic active hepatitis is made primarily on clinical grounds. In our opinion the picture is quite as distinctive as that of many other generally accepted clinical diagnoses<sup>1</sup>. The condition is characterized by relatively severe symptoms, liver tenderness and

a tendency to remission and relapse. Exercise aggravates the symptoms, makes manifest or increases liver tenderness and if sufficiently prolonged increases laboratory evidence of liver dysfunction. The fact that a relapse can be produced by exercise establishes the presence of liver disease on an objective basis and makes it possible to determine whether symptoms are related to the liver or not. The presence of only minimal objective findings after a period of bed rest has often lead to confusion and to the conclusion that symptoms were functional in nature. Finally, it must be remembered that the severity of the liver injury must be determined principally by laboratory methods.

In our series the incidence of chronic active hepatitis has been dependent upon the elapsed time from onset of the acute disease. Thus 4 months after acute hepatitis with jaundice 10% still had active hepatitis whereas after one

TABLE 2

*Symptoms in 91 Consecutive Cases of Chronic Active Hepatitis of Four Months to Four Years Duration.  
37% had Bilirubinemia*

	per cent
Lassitude and Fatigue.....	99
Anorexia.....	73
Flatus.....	71
Liver Ache.....	52
Headache.....	49
Cramps.....	49
Diarrhea.....	15
Weight Loss Over 10 Pounds.....	14

year only 3% fell in this group. The remainder either became inactive or recovered.

The frequency of the more common symptoms is shown in Table 2 and it will be noted that many symptoms occur which are not seen in inactive hepatitis. Lassitude is the most disabling as well as the most characteristic symptom. It does not seem to be due primarily to weakness or easy fatigue but is rather a kind of inertia. Other less common symptoms are shown in table No. 3. Associated with right upper quadrant distress is often right lumbar ache and occasionally pain deep in the right chest. The other symptoms are ones about which there might be some question but which we feel to be definitely part of the disease. They have frequently been observed to develop or to disappear in close correlation with laboratory and other evidence of liver disease. Competent psychiatric opinion has been obtained in all doubtful cases and has served to substantiate our opinion. The peculiar mental state observed in these patients is superficially similar to an anxiety state and is often associated with such vasomotor phenomena as hot flashes, pruritus

and even urticaria from heat and oral hyperthermia. In addition we have observed such endocrine disturbances as menorrhagia in the female and impotence, gynecomastia and spider angioma in the male.

The physical finding of a tender liver especially by fist percussion is of prime diagnostic importance although not always easy to evaluate. When the pain so produced develops after a short latent period of a few seconds and persists for several minutes or hours, we believe that the observer can be quite certain that true liver tenderness is present. Tenderness in the right costovertebral angle as we originally described<sup>6</sup> is further valuable confirmation of liver tenderness.

The final characteristic feature of chronic active hepatitis is the response to exercise. An aggravation of symptoms and an increase in liver tenderness develops not immediately but rather the next day and characteristically persists for several days or more even though no exercise is taken. When the

TABLE 3  
*Less Common Symptoms and Findings in Chronic Active Hepatitis*

*Pain*

Severe abdominal, deep right chest pain, right lumbar ache

*Anxiety State*

*Vasomotor Disturbances*

Pruritus and urticaria from heat or emotion

Hot Flashes

Oral hyperthermia

*Endocrine Disturbances*

Menorrhagia

Impotence, gynecomastia and spiders

the reaction is sufficiently severe, laboratory findings will also become more marked. This response to exercise along with its counterpart, improvement from bed rest, is most helpful in distinguishing the true psychoneuroses which are affected in an opposite manner.

The prognosis in this group is uncertain although some cases recover or become inactive in a year. Others continue to have exacerbations and remissions for at least four years, although the exacerbations may occur at gradually increasing intervals. Some, however, develop progressively more severe liver disease and eventually cirrhosis. One special type of case should be mentioned, namely what Watson calls cholangiolitic hepatitis or cirrhosis<sup>11</sup>. In this condition there is a persistent bilirubinemia involving both the direct and indirect types of bilirubin, a markedly elevated serum alkaline phosphatase as in obstruction and often at first a negative cephalin-cholesterol flocculation test.

It is of interest that chronic active hepatitis is frequently mistaken for a psychoneurosis. In fact we have never failed to find a number of such cases

in making rounds on the neuropsychiatric service in the army. Laboratory evidence of liver disease alone, unless marked, is not sufficient to establish the diagnosis because obviously the two may occur together. The clinical differentiation is not difficult providing the previously mentioned criteria are kept in mind. Too often the clinical picture is ignored and inadequate laboratory tests are relied upon as in the reports of Benjamin and Hoyt<sup>12</sup> and Caravoti<sup>13</sup>. In addition to psychoneurosis a primary diagnosis of gastritis or irritable bowel are often made when in fact they are secondary to liver disease. Cholecystitis is frequently suspected because of a dim or absent gall bladder shadow due to an inability of the liver to secrete the dye<sup>14</sup>.

#### SUMMARY

It is pointed out that an appreciation of the clinical picture is essential to a proper evaluation of the patient with chronic hepatitis. Laboratory and histological data alone are inadequate for this purpose and their value at present is overemphasized. The correlation of symptoms, liver tenderness and response to exercise are shown to provide an objective clinical yardstick.

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## DISCUSSION

DR. LEON SCHIFF (Cincinnati, Ohio): I have listened with much interest to these various presentations and feel more and more convinced that the best and most information on this subject is going to be obtained by a combination of clinical study, laboratory tests, liver biopsies, preferably needle biopsies of the liver, and the physiological approach, as being carried out by Dr. Ingelfinger.

I admit, and I think everyone does, that most cases of acute hepatitis recover completely, and I think that everyone admits that some cases develop cirrhosis. There are two types of sequelae that interest us at the present time. One is active chronic hepatitis without fibrosis; the other is the type in which there is fibrosis early, perhaps within a few weeks or more after the acute episode. In the latter form, the question arises as to whether the fibrosis will heal (as a scar) or resolve, or go on to a chronic active hepatitis with cirrhosis.

One patient whom we are observing at present, and I regret to say we don't have his slides, had a typical homologous serum hepatitis and was biopsied sixteen day after the onset of jaundice. The biopsy revealed in addition to the characteristic changes of acute hepatitis some periportal fibrosis.

The patient improved in a laboratory sense, and at a biopsy taken one month later, or six weeks after the onset of jaundice, there was a disappearance of the intralobular changes, but a persistence of the periportal fibrosis. He is much better but what is going to happen to him? He will probably recover, but we are interested to see what a future biopsy will reveal.

I should like to show a slide on another example of homologous serum hepatitis. You see jaundice developed on the 25th of July 1947. There was an elevated serum bilirubin, the cephalin flocculation was positive, there was a slightly increased thymol turbidity, and the serum alkaline phosphatase was normal.

[Slide]—In the course of time his jaundice has disappeared, his cephalin flocculation is listed as 3-plus on April 2, 1948 but is now negative—the first part of this week. You see his thymol turbidity has gradually risen to nine units in the first part of this month. The thymol flocculation is still 4-plus. He no longer has any bromsulphalein retention.—[Slide] Biopsy taken about two weeks ago, about eight to nine months after the onset of hepatitis, shows persistent periportal infiltration with lymphocytes and histiocytes, some focal intralobular change and no fibrosis.

Volwiler and Elliott have shown by liver biopsy that a patient can have signs of persisting active inflammation for forty-two months following acute hepatitis without any fibrosis.

I want to take exception to Dr. Strumia's statement. I believe his young patient should have needle biopsy, because we have found it quite safe, having done four hundred cases without any fatality or serious consequence. We do not think the procedure ought to be turned loose as yet, but ought to be done by one or two men trained in any one given clinic.

I should like to ask Dr. Capps if he will say a word about the mechanism of tenderness of the liver in patients who do not have hepatic enlargement and presumably stretching of Glisson's capsule.

DR. DAVID H. ROSENBERG (Chicago, Ill.): The papers just presented are of great interest in the elaboration and elucidation of the sequelae of acute hepatitis. However, the interpretation of the clinical significance of the sequelae is difficult and varies greatly with different patients presenting identical symptoms and signs. It should be emphasized that the vast majority of non-fatal cases of acute hepatitis, treated adequately according to present-day standards, progress to clinical recovery. Yet, in as many as 50 per cent or more of the patients, minimal residual symptoms persist for variable periods of time after the disappearance of the jaundice.

In this latter symptomatic group we have found that tests of liver function frequently yield negative results, or that only one test is abnormal. Periportal infiltration is present on histologic examination of the liver tissue of some of these, while in others, even in the presence of mild icterus, the parenchyma and periportal spaces are entirely normal.

Dr. Tumen mentioned that in some of the cases hypoprothrombinemia was found after apparent recovery from hepatitis. I should like to ask him whether prothrombin response tests were made following the administration of Vitamin K, for we know that in Vitamin K deficiencies, which may develop in patients during the course of acute hepatitis, hypoprothrombinemia may be observed in the absence of liver insufficiency.

Dr. Strumia's report of several cases is of interest and adds to our accumulated knowledge, but it would be of considerable value and most desirable if we had been able to have studies of the histological findings in these cases.

The finding of hepatic tenderness or of a single abnormal liver function test, while important in the recognition of residual hepatitis, should not necessarily be construed as indicative of the presence of residual hepatitis, for in some patients the liver histologically may be found normal.

A history of jaundice in the distant past, elicited in patients with the histologic picture of periportal fibrosis *per se*, has been regarded by some authors as evidence in support of a preexisting virus hepatitis, but I do not believe that this conclusion is justified in all cases, for other conditions, notably dietary deficiencies and excesses, are also known to produce this microscopic picture.

The duration and persistence of periportal inflammation seem to be related to the intensity and duration of the icterus, to the virulence of the infecting virus, or to the tissue resistance of the host, or to all of these factors. Whether or not a given instance of acute hepatitis will progress to the ultimate development of *cirrhosis* is dependent upon the integrity of the silver-staining reticulum fibers, which constitute the stroma network of the liver. These fibers represent a scaffolding along which regenerating liver cells develop in the restoration of the liver lobule, and without which complete loss of normal architecture of the liver ensues, with the development of cirrhosis. It is noteworthy that in the usual case of epidemic hepatitis, this reticulum framework remains intact. It is apparent that more universal and serial histologic studies will be required in order to determine the incidence of residual chronic active hepatitis.

Finally, judicious care must be exercised in ascribing the symptoms following acute hepatitis to the histologic findings of periportal infiltration, for the latter may be

found in individuals presenting no symptoms, and may be consistent with normal activity.

DR. FRANK W. HARTMAN (Detroit, Mich.): I should like to confine my discussions to three points; first, to the matter of terminology. I notice this morning the symposium is entitled "acute hepatitis." There is a great deal of misunderstanding and a great deal of confusion about terminology. It was emphasized very strongly in a personal instance I had, where I quoted Dr. Mallory as preferring the term "epidemic hepatitis," and stated that was the official terminology of the U. S. Army. The clinicians jumped up and handed me a pamphlet issued by the U. S. Army in which they advised the name "infectious hepatitis," so that there is that difference of opinion in the Army, and I think in civilian practice it is still much more confusing.

It seems to me the term used by Dr. Capps is to be preferred, "virus hepatitis," or "viral hepatitis," to distinguish from other types of acute hepatitis.

Dr. Mateer and I have introduced another "acute hepatitis" this morning, that is, "acute infiltrative type of hepatitis," and that certainly is not of viral origin.

In the second place, the pathological differentiation should be emphasized. Dr. Strumia quoted four cases and gave us a nice pathological picture in the fourth case, that, grossly and microscopically, is typical of the viral type of hepatitis and should be kept in mind to differentiate it from other types of cirrhosis.

The third point is: the American Red Cross has instituted a new program for the collection and stockpiling of plasma. Are clinicians going to stand by and see this plasma distributed again without being sure that the material is going to be sterile and that we are not going to have again 4.5 per cent or more cases of acute viral hepatitis with a mortality of 10 per cent?

DR. JAMES L. BORLAND (Jacksonville, Florida): I believe that in papers dealing with chronic hepatitis the cases should be grouped in the rough categories which seem indicated by present evidence; otherwise the discussion has no meaning. A great many clinicians who observed outbreaks of epidemics of hepatitis in the Mediterranean and Pacific areas noted clinical differences in these cases and in those seen in private practice. In my own experience in an investigation of 1500 cases occurring on a small South Pacific island 75% of the cases showed a definite clinical pattern: An initial fever, a period in which there were no symptoms lasting from four to ten days, followed by the onset of liver tenderness, anorexia, jaundice. Therefore, some subdivision can be made on clinical grounds. There is evidence to indicate that there is a difference in the mode of transmission of the strains of virus. This results in some difference in the disease, even affecting the liver function tests.

The stage at which the disease is observed, even judging from duration alone, is certainly important. The substance affecting the liver function tests may differ in the acute and chronic stage.

I should like to emphasize Dr. Capps' point that in the early acute case of hepatitis the general condition of the patient and the response of this condition to activity is the important thing. If convalescence is well organized, the response of the liver function tests to the patient's daily activity is the crux of the matter.

DR. MOSES PAULSON (Baltimore, Md.): In 1934 Silver and I, in the Archives of Internal Medicine, for the first time pointed out the fact that following catarrhal jaundice in individuals who had for as far back as eighteen years previously a catarrhal jaundice, evidences of residual hepatic damage exist, as shown by means of the bilirubin excretion test, the most delicate liver function test that we have available, and which has apparently been forgotten. We also pointed out in that communication that most of these people had symptoms analogous to those pointed out by Dr. Capps this morning, and that in those individuals in whom symptoms were present, the bilirubin test was positive, and in the individuals who manifested no symptoms at all, the bilirubin excretion test was negative. It was also pointed out while we recognized the fact that some of these people, at any rate, may eventually develop cirrhosis, the fact remained that even after fifteen or eighteen years following acute hepatitis, none of them had developed cirrhosis.

The point I wish to emphasize is that it would do us good to use more frequently the bilirubin excretion test. By means of much more simple methods we can acquire the same data which we have today by more elaborate methods.

DR. J. EDWARD BERK (Philadelphia, Pa.): Several reports in the literature have implied that infectious hepatitis plays an important role in the production of cirrhosis, because of the frequency with which a history of previous jaundice can be obtained in the individuals in whom cirrhosis was established, but even if it is granted that every one of the occurrences of jaundice in the past represented an episode of acute hepatitis, it is important to us to have demonstrated that this evidence in the cirrhotic patient is significantly greater than in the population at large, if we are to infer that hepatitis may play an important role in the production of cirrhosis.

I am aware of nobody supplying just what the incidence of infectious hepatitis with jaundice is in the population at large. We are now in the process of making a complete survey among medical personnel at three universities, the University of Oregon, the University of Chicago, and Temple University. Unfortunately figures from the University of Oregon are not here. Members from the University of Chicago are present, and we have completed ours at Temple.

To date we have surveyed over 1000 such people, varying from seventeen to forty. It is of interest then to note that the occurrence of infectious hepatitis with jaundice in each of those patients who submitted a history of having had jaundice was carefully and individually examined. The incidence of hepatitis with jaundice in this apparently normal group of people, was 6.6 per cent.

We might figure this magnitude or one close thereto must be significantly greater in cases with cirrhosis, if we are to conclude that from jaundice with hepatitis in the past plays an important role in the production of cirrhosis.

DR. RICHARD B. CAPPS (Chicago, Ill.): In answer to Dr. Schiff's question regarding the mechanism of tenderness of the liver when the liver is not enlarged, I do not have any really satisfactory explanation. I presume that inflammatory changes in the liver might affect the capsule and possibly cause tenderness, but this is not a very satisfactory explanation.

I should like to say in regard to some of Dr. Rosenberg's remarks that we don't believe that tenderness of the liver alone should be automatically accepted as evidence of liver disease. Naturally, it is not a simple matter to evaluate liver tenderness. Individuals who are sensitive to pain, may apparently have liver tenderness with a normal liver. In questionable instances, the nature of the pain, the presence of costovertebral angle tenderness, and finally the response to exercise, I think will settle the question.

DR. HENRY J. TUMEN (Philadelphia, Pa.): There have been a few points raised during the course of the discussion which require some specific comment. One of these is in reference to the prothrombin determinations. Because this laboratory procedure is one that is often unreliable, due to many circumstances, our own results were viewed by us with a great deal of suspicion and reviewed and repeated many times by the same technician. I believe that they are reliable.

So far as the response to Vitamin K administration is concerned, as noted on one of our slides, we were able to give Vitamin K to five of the eight patients who had hypoprothrombinemia. We observed in them that the response was not what could be expected of an individual who had a normally functioning liver in respect to prothrombin manufacture.

I might also say, in comment, that we could observe no relation between the laboratory evidence of continued slight liver dysfunction in our patients and the history, in so far as this could be determined, regarding the severity or prolongation of the original attack of hepatitis.

Dr. Paulson has raised the question of bilirubin excretion test, or bilirubin tolerance test, about which he and Dr. Soffer reported many years ago. I, also, regret that this test is not used more widely. I am sorry that neither Dr. Neefe nor Dr. Reinhold has appeared to enter this discussion. In using that test on numbers of normal individuals, however, they were unable to standardize the results, and felt that it was a test that was extremely difficult to use and to accept in every instance.

Finally, I would like to say this, that the big problem concerning hepatitis, as Dr. Capps has already mentioned, is the fact that some of these patients very probably do go on later in life to develop chronic severe liver disease of a type which warrants a diagnosis of cirrhosis. The big problem which we, as clinicians have, is to try to select those patients early in their course so that whatever treatment is available can be applied. Unfortunately, at the present time we have no way to select these patients, and I myself do not believe that there is any single laboratory procedure which at this time will help us to distinguish these patients from others who have had hepatitis.

All our ideas about hepatitis and its results have to be very tentative. A great deal of time will be necessary before we can settle many of the questions which have been raised. I should like to suggest to those who are going to make the program for this society ten or fifteen years from now, that we have a symposium on this, similar to the one to be held on vagotomy tomorrow, so that our ideas can be correlated again and evaluated after many more years have passed.

DR. MAX M. STRUMIA (Bryn Mawr, Pa.): One point I want to make is that we have tried as much as has been possible to obtain liver biopsies, but, unfortunately, our requests are being turned down in a number of cases. They are often turned down because of the fear in the attending physician that something may happen. I hope that that attitude will be dissipated in the future.

Another point which I want to make has been brought out by the question about jaundice. We feel that jaundice in a patient with hyperemia may be related, and that has been observed by others and by us. In patients that have recovered from attacks of infectious hepatitis there appear to be islands of liver cells either left over or newly formed, which are anatomically almost isolated from the rest of the liver and therefore these may not participate in bile elimination.

PRESIDENT BOCKUS: Dr. Strumia, if you don't mind, I wish you would try to answer Dr. Hartman's question about what we are going to do about homologous serum jaundice.

DR. STRUMIA: I hoped you wouldn't insist on my attempting to answer Dr. Hartman's question, but since it is invited, I shall be delighted to let you have my opinion.

We are conducting a rather extensive survey of intravenous administration of whole blood, and plasma. We have so far received something like nine hundred returns on the patients who have received these transfusions. It is a gigantic task because the reports which have appeared in the State of New York related to injection of plasma from the American Red Cross are certainly not critical enough to be taken into serious consideration, but there is one point we have definitely established in three individual instances, and these are as follows:

In all these three cases the patient developed jaundice following the injection, within six months, of a pooled lot of plasma. We were able to determine in these three instances the correct preceding status of all donors, and also the follow-up of all patients who received the same blood. We were unable to detect any instance of jaundice in the individuals who furnished the blood or in the other recipients of the same lots.

I repeat, it is a tremendous task because there are too many people going from patients to doctors and from doctors to patients. We feel it is worth while continuing. It is only by exceedingly careful evaluation that we can answer Dr. Hartman's question. We are ourselves quite detached from the matter, whether it is good or whether it is bad. We are not discussing the use of pooled plasma, but I repeat, in three cases where we were lucky enough to trace every one of the donors and every one of the recipients, we found no instance where two recipients developed jaundice from the same pool. Whether it is homologous serum jaundice, I cannot answer. We can simply say jaundice developed in these three cases within six months of receiving a single lot of pooled plasma.

We can tell you that the clinical manifestations were definitely those of viral hepatitis, and that will be as much as we can tell you today. Perhaps in a year and a half we will be delighted to let you have the rest of the story.

## TOTAL FECAL SOLIDS, FAT AND NITROGEN. IV. A STUDY OF PATIENTS WITH CHRONIC RELAPSING PANCREATITIS\*†

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### INTRODUCTION

When one or more of the three diagnostic sequelae of chronic relapsing pancreatitis, namely, diabetes, calcification and gross steatorrhea, are demonstrable, the diagnosis seldom is difficult. However, when the patient is seen in the interval between the acute episodes, when the values for enzymes in the serum are not elevated and when the sequelae have not developed, a presumptive diagnosis may be made upon certain clinical features of the acute episodes and by exclusion of other diseases of the upper part of the abdomen; the diagnosis may be proved only by demonstration of deficiency of external pancreatic secretion. Dependable methods for demonstration of insufficiency of external pancreatic secretion become invaluable in the diagnosis of the disease in such cases.

Intake-excretion studies in 20 cases of chronic pancreatitis herein reported were carried out to determine the fecal solids, fat and nitrogen in chronic relapsing pancreatitis and to determine the value of such studies in establishing the existence of insufficiency of external secretion and the diagnosis of chronic pancreatitis especially in cases in which the gross sequelae of the disease are absent.

### SUBJECTS STUDIED

Intake-excretion studies were carried out on patients with varying degrees of pancreatic destruction secondary to chronic relapsing pancreatitis and the results were compared with those obtained in a group of 11 normal persons previously reported by some of us<sup>1</sup> (tables 1, 2 and 3). The cases fall readily into two groups. In group 1 were placed 10 cases in which calcification and diabetes were not demonstrable (table 2). In group 2 were placed 10 cases

\* Read at the meeting of the American Gastroenterological Association, Atlantic City, New Jersey, April 30 to May 1, 1948.

† Abridgment of thesis submitted by Dr. Dornberger to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

in which calcification or diabetes or both were demonstrable (table 3). In 7 of the 10 cases of the latter group, gross steatorrhea was suspected because of the history of diarrhea, of liquid fat in the feces or of bulky stools that were fatty in appearance. The degree of pancreatic destruction may be assumed to be greater in the cases of group 2.

#### PROCEDURE

The procedure was the same as that which has been described previously<sup>2</sup>. All studies were carried out in the metabolic study unit and the period of study was three to six days, depending on the time interval necessary for passing the carmine markers.

TABLE 1

*The Total Solids, Fat and Nitrogen Per Day in the Feces of Normal Persons on the Standard Test Diet\**

	TOTAL SOLIDS	FAT			NITROGEN	
		Total	Per cent of total fecal solids	Per cent of ingested fat	Total	Per cent of ingested nitrogen
Average†.....	27.6 ± 2.2	4.1 ± 0.5	14.5 ± 1.1	4.0 ± 0.5	1.7 ± 0.1	8.9 ± 0.8
Standard deviation....	7.3	1.5	3.7	1.7	0.4	2.6
Minimum.....	13.6	1.8	9.3	1.8	0.8	4.3
Maximum.....	39.1	6.7	19.6	6.6	2.5	13.2

\* 101.6 gm. of fat and 117.5 gm. of protein (18.8 gm. of nitrogen) per day were ingested.

† The figure after the ± is the standard error of the mean.

#### DIET

The moderately high fat diet used in a previously reported study of normal subjects was given each patient<sup>1</sup>. The calculated average daily intake was as follows: fat 101.6 gm., protein 117.5 gm. and carbohydrate 269.6 gm. This furnished 2,463 calories each day. It was required that all food be eaten.

#### LABORATORY METHOD

The methods of determining fecal total solids, fat and nitrogen have been described elsewhere<sup>2</sup>. Fecal fat was determined by a method essentially that of Saxon<sup>3</sup> and fecal nitrogen was determined by the Kjeldahl procedure.

#### RESULTS

*Group 1. Chronic relapsing pancreatitis without apparent sequelae.*—The data for this group of cases have been summarized in table 2 and compared with similar data obtained for normal persons (table 1).

Fecal solids.—The average daily weight of the total fecal solids was 25.1 gm. This value is not very different from that (27.6 gm.) obtained for normal persons ingesting the same diet; the difference between the two was not statistically significant. In 9 of the 10 cases the value for total fecal solids fell within the normal limits.\* In 1 of the 10 cases (case 2) the average daily weight of the total fecal solids was 8.5 gm.; since this value was more than two times the standard deviation below the normal mean, it is to be considered presumptively abnormal, although it may have been due to the marked con-

TABLE 2

*The Total Solids, Fat and Nitrogen Per Day in the Feces of 10 Patients with Chronic Relapsing Pancreatitis Without Apparent Sequelae on the Standard Test Diet*

CASE	TOTAL SOLIDS gm.	FAT			NITROGEN	
		Total	Per cent of total solids	Per cent of ingested fat	Total	Per cent of ingested nitrogen
1	30.4	3.1	10.2	3.1	1.7	9.0
2	8.5	3.3	38.8	3.3	1.2	6.4
3	24.5	3.3	13.6	3.3	1.8	9.5
4	17.8	3.5	19.4	3.5	1.2	6.4
5	23.1	3.8	16.5	3.7	1.4	7.4
6	23.0	4.1	18.0	4.0	1.6	8.5
7	28.7	4.8	16.7	4.7	1.4	7.4
8	25.8	5.1	19.8	5.0	1.9	10.1
9	36.5	6.3	17.2	6.2	1.8	9.5
10	32.4	7.5	23.1	7.4	1.3	6.9
Mean*	$25.1 \pm 2.5$	$4.5 \pm 0.5$	$19.3 \pm 2.4$	$4.4 \pm 0.5$	$1.5 \pm 0.1$	$8.1 \pm 0.4$
Standard deviation...	7.9	1.5	7.7	1.4	0.3	1.4
Difference from normal†.....	$2.5 \pm 3.45$	$0.4 \pm 0.65$	$4.8 \pm 2.45$	$0.4 \pm 0.6$	$0.2 \pm 0.16$	$0.8 \pm 2.9$

\* The figure after the  $\pm$  is the standard error of the mean.

† Difference between the normal mean and the mean of this group.

stipation encountered in the study of this patient. A value this low was not found in any of the normal subjects.

Fecal fat.—The average daily weight of the total fecal lipoids was 4.5 gm., which is not very different from that (4.1 gm.) obtained for normal persons ingesting the same diet. The difference is not significant. In 9 of the 10 cases the values fell within normal limits but in one case (case 10), the value was 7.5 gm.; since this value was more than two times the standard deviation above the normal mean, it may be considered presumptively abnormal. A value this high was not found in any of the normal subjects. The average

\* Normal mean  $\pm$  two times the standard deviation was considered normal limits.

daily value for the percentage of ingested fat found in the feces followed the same pattern as that for values for total lipoids in grams. The average (19.3 gm.) for the percentage of total dried fecal solids which was fat was greater than the average in normals (14.5), but the difference between the two is not statistically significant. In 2 cases, the percentage of fecal solids which was fat (38.8 and 23.1 per cent, respectively) was greater than the upper limit of normal. These values, being greater than twice the standard deviation above the normal mean, can be considered presumptively abnormal. However, in 1 case, the high value arose from the abnormally low value for fecal solids which, as we have suggested, was probably due to constipation. In another study in this case, external pancreatic secretion as measured by the secretin test was normal and it is doubtful that the high value for total fecal solids which was fat was due to diminished external pancreatic secretion. In the second case, the high value can be accounted for by the abnormal loss of fat.

Fecal nitrogen.—The average daily weight of fecal nitrogen was 1.5 gm. This figure is not very different from that (1.7 gm.) obtained for normal persons ingesting the same diet. The difference between the two is not significant. The average daily weight of each of the 10 patients fell within normal limits.

*Group 2. Chronic relapsing pancreatitis with sequelae.*—Data for this group of cases have been summarized in table 3. The sequelae present have been indicated in the same table.

Fecal solids.—The average daily weight (53.1 gm.) of the total fecal solids for this group was nearly double that (27.6 gm.) obtained for normal persons ingesting the same diet. The difference between the two is statistically significant. In 7 of the 10 cases, the value was definitely greater than any obtained in the normal, but in only 5 cases the values were more than two times standard deviation above the normal mean and are, therefore, to be considered presumptively significant.

Fecal fat.—The average daily weight (21.6 gm.) of fecal fat was more than five times as great as that (4.1 gm.) obtained for normal persons ingesting the same diet. The difference between the two is statistically significant. In all 10 cases, the value for average daily fecal fat was greater than that obtained in any of the normal subjects examined. In 7 of the 10 cases the values for average daily weight of fecal fat were much more, but in the remaining 3 they were only slightly more, than two times the standard deviation above the normal mean. In all 10, the values are to be considered presumptively abnormal. The values for the percentage of ingested fat found in the feces and for the percentage of fecal solids which was fat followed a similar pattern.

Fecal nitrogen.—The average daily weight of nitrogen (3.2 gm.) for the 10 patients was nearly double that (1.7 gm.) obtained for normal persons ingest-

ing the same diet. The difference between the two was significant (table 3). In 5 of the 10 cases, the value exceeded the highest value obtained in any normal subject studied. In the same 5 cases the average daily values were more than two times the standard deviation above the normal mean and are, therefore, to be considered presumptively abnormal.

TABLE 3

*The Total Solids, Fat and Nitrogen Per Day in the Feces of 10 Patients with Chronic Relapsing Pancreatitis with Sequelae on the Standard Test Diet*

CASE	TOTAL SOLIDS	FAT			NITROGEN		SEQUELAE*		
		Total	Per cent of total solids	Per cent of ingested fat	Total	Per cent of ingested nitrogen	D	C	S
	gm.	gm.			gm.				
11	34.3	7.7	22.4	7.6	1.8	9.5	0	+	0
12	37.2	8.1	21.8	8.0	1.7	9.0	0	+	0
13	35.0	8.3	23.7	8.2	1.9	10.0	+	+	0
14	52.3†	16.8	30.8	16.7	3.7	19.7	++	+	+
15	39.7	18.2	45.8	18.0	2.2	11.7	++	+	+
16	39.2	19.4	50.0	19.2	2.1	11.2	++	+	+
17	53.9	26.5	50.0	26.3	3.4	18.1	0	+	+
18	66.5†	27.1	40.7	26.9	4.2	22.3	0	+	+
19	87.6	39.4	44.9	39.1	5.5	29.2	++	+	+
20	85.4	44.1	51.6	43.8	5.6	29.8	++	+	+
Mean.....	53.1 ± 6.4	21.6 ± 4.0	38.2 ± 3.9	21.4 ± 4.0	3.2 ± 0.5	17.1 ± 2.6			
Standard deviation.....	20.3	12.8	12.3	12.7	1.5	8.1			
Difference from normalf.....	25.5 ± 6.6	17.5 ± 3.87	23.7 ± 3.8	17.4 ± 3.8	1.5 ± 0.5	8.2 ± 2.6			

\* D = diabetes; C = calcification; S = gross steatorrhea (on clinical basis alone); + = present; 0 = absent.

† Average of two tests.

‡ Difference between normal mean and mean of this group of cases.

#### COMMENT

Several points of interest arise from a study of these data.

1. The value for average daily total fecal solids did not exceed the normal upper limit in any of the 10 cases of chronic pancreatitis without sequelae, but it did do so in 5 of the 10 patients with sequelae. The values became abnormally high only when extensive disease of the pancreas was present. Only in these 5 cases did analysis of the feces for total solids demonstrate insufficiency of external pancreatic secretion, and in these same cases the existence

of insufficiency of external pancreatic secretion already was known because steatorrhea recognizable by gross inspection of stools was present. Abnormally large amounts of fecal solids were found only when calcification and gross steatorrhea with or without diabetes were present to insure a correct diagnosis. Analysis of feces for total solids did not furnish diagnostically significant data in these 20 cases.

2. The percentage of total fecal solids which was fat exceeded the limits of normal in 2 of the 10 patients without sequelae and in 10 of 10 cases with sequelae. In 1 of the 2 patients without sequelae in which the percentage was abnormal, the abnormally high percentage, which appears to have been due to an abnormally low value for fecal solids and not due to abnormal losses of fat and nitrogen, seemed to point to an insufficiency of external pancreatic secretion, however, this insufficiency was not demonstrable by other means and was diagnostically misleading. In the other case in which the percentage was high, the value for fecal fats likewise was high. Determination of percentage of total fecal solids which was fat added nothing diagnostically to the data obtained by determination of fecal fat.

3. Abnormal steatorrhea, on the basis of fecal analysis alone, was found in only 1 case of chronic pancreatitis without calcification or diabetes or both (group 1), but was demonstrable in all 10 patients with calcification or diabetes or both diabetes and calcification (group 2). Excessive amounts of fecal fat seemed to appear when extensive destruction of the pancreas had taken place.

4. The percentage of ingested fat lost in the feces followed the same pattern as did the fecal fat in grams per day.

5. Of the total of 20 cases in which intake-excretion studies were conducted, in 7 (cases 14 to 20 inclusive) the demonstration of abnormal steatorrhea merely served to confirm the already recognized gross steatorrhea and insufficiency of external pancreatic secretion, but in another 4 cases (cases 10 to 13 inclusive) such studies served to demonstrate an otherwise unrecognized slight degree of steatorrhea and insufficiency of external secretion. In the remaining 9 cases (cases 1 to 9 inclusive), the study failed to detect an insufficiency of external secretion. It appears that carefully conducted intake-excretion studies are of value in detecting minor degrees of external insufficiency.

6. Demonstration of steatorrhea in cases 11 to 20 inclusive had little diagnostic value. In these cases the combination of recurring episodes of pain plus calcification or calcification and diabetes was adequate for correct diagnosis. In case 10, in which calcification and diabetes were not present, the demonstration, by fecal analysis, of slightly abnormal steatorrhea served to confirm a presumptive diagnosis based on history. It appears that in the absence of diabetes and calcification and in the absence of elevated values for

the serum amylase and lipase during acute seizures or in the interval between acute seizures, carefully conducted intake-excretion determinations of fat lost may occasionally provide valuable diagnostic data.

7. Abnormal azotorrhea was found only when calcification with or without diabetes was present and only when the losses of fat were sufficient to produce stools fatty enough to be recognized as steatorrheal by gross inspection.

8. Analysis of feces for total fat appears to give more information in the early diagnosis of pancreatic insufficiency and of pancreatic disease than does analysis for total fecal solids or fecal nitrogen. This suggests that, as insufficiency of external secretion progresses, excessive fecal fat appears before excessive fecal nitrogen.

Abnormal azotorrhea does not always accompany an abnormal steatorrhea and is not necessarily a part of the picture of insufficiency of external pancreatic secretion.

9. The percentage of ingested fat lost ranged up to approximately 44 per cent. The percentage of fat lost was less than that which occurred in some cases of complete absence of pancreatic juice studied by some of us<sup>4</sup>; thus, after resection of the head of the pancreas, the percentage of ingested fat lost by 3 patients ingesting the same diet ranged from 55.4 to 65.1 when the pancreatic duct was ligated, but the percentage of ingested fat lost by 2 patients after total pancreatectomy varied from 35 to 70<sup>5, 6</sup>. This suggests that pancreatic insufficiency approached completeness only in 1 or 2 of these 20 cases. However, because partial gastrectomy (posterior Polya anastomosis) alone is followed by excessive loss of fecal fat<sup>7</sup>, partial gastrectomy which is part of the operation of partial or complete pancreatectomy may account for some of the loss of fat following partial or complete pancreatectomy and may narrow the difference between the value in absence of the pancreatic juice from the intestine after pancreatectomy and the value in chronic pancreatitis.

10. Previous investigators<sup>8-14</sup>, have reported greater percentages of ingested fat lost. Intake-excretion studies on 17 previously studied patients with pancreatitis have been listed in table 4. In 12 of the 16 cases in which percentage of ingested fat lost was determined, the value was above 50. Differences in the degree of destruction of the pancreas and of completeness of loss of external secretion in our cases and in those of previous investigators may be advanced in explanation of the differences in results. However, because loss of fat reported by others was greater in many cases than that encountered in cases of complete absence of pancreatic juice from the intestine, it seems possible that some factor other than absence of pancreatic juice was superimposed.

11. The percentage of ingested nitrogen lost in the feces ranged as high as 29.8. The percentage of ingested nitrogen lost was less than that which oc-

TABLE 4  
*Results of Intake-Excretion Studies in Reported Cases of Chronic Pancreatitis*

AUTHOR	DATE	CHRONIC PANCREATITIS WITH	METHOD OF DIAGNOSIS*	JAUNDICE†	DAYS OF STUDY	MARKERS	DAILY INTAKE		DAILY FECAL VALUES										
							Fat	Nitrogen	Total solids		Total fat		Percentage of fecal fat as			Fat, per cent of			
									gm.	gm.	gm.	gm.	Fatty acids	Soap	Neutral fat	Ingested	Dry solids	Total	Per cent of ingested
Harley <sup>11</sup>	1895	Calculi	C	—	4	+	196.9	13.1	143.8									gm.	40.0
Brugsch <sup>9</sup>	1906	Ab-scess	A	—	3	+	49.0	6.1		29.3	47.3	43.8	17.9	59.7	46.4	1.3		5.3	21.3
		Ab-scess	A	+	3	+	51.0	6.2		36.8	59.5	23.1	17.4	72.2	48.4	1.8		28.6	
		Calculi with duct ob-struction	A	—	3	+	72.0	6.2		50.5	62.5	20.5	17.0	70.1	53.7	1.6		25.4	
Tileston <sup>14</sup>	1912	Diabetes	C	—	3	+	67.0	15.2	123.0	48.4	59.0	5.2	35.8	72.7	39.6	9.5			62.2
Pratt <sup>12</sup>	1912	Duct ob-striction	C	—	3	+	152.0	16.7	146.0	89.5	37.4	6.0	56.6	58.9	61.3	8.5			50.9
Thaysen <sup>13</sup>	1928	Calculi	A	—	3	+	136.0	19.8		101.0								9.6	53.9
		Calculi	C	—	3	+	95.0	17.6		132.5								16.8	97.0
Beazell, Schmidt and Ivy <sup>8</sup>	1941	Latent syphilis	C	—	3	+	112.0	10.3										6.0	58.0
		Calculi	C	—	3	+	112.0	10.3		44.5								7.9	77.0
		Calculi	C	—	3	+	112.0	10.3		94.0								13.3	129.1
		—	C	—	3	+	112.0	10.3		84.7								4.2	40.0
Percentage of dried feces																			
Frazer <sup>10</sup> and co-workers	1946	—	A	—	2	+	50.0			40.9	27.8	21.0	2.4	81.8	51.2				
		—	S	—	2	+	20.0			12.5	20.0	9.6	6.0	62.5	35.6				
		—	A	—	2	+	50.0			6.6	5.8	4.9	1.8	13.2	12.5				
		—	S	—	3	+	50.0			8.7	7.3	8.9	11.2	17.4	27.4				
		—	A	—	2	+	50.0			4.6	10.3	4.7	3.7	9.2	18.7				

\* A = autopsy; C = clinical; S = surgical.

† + = present; — = absent.

curried in patients with absence of pancreatic secretion from the intestine studied by two of us<sup>4</sup>; thus after resection of the head of the pancreas and liga-

tion of the pancreatic duct, the percentage of nitrogen lost by 3 patients ingesting the same diet ranged from 36.0 to 49.2. Similarly, after total pancreatectomy the percentage of ingested nitrogen lost in the feces of 2 patients was respectively 38 to 55 and 30 to 34<sup>6, 9</sup>. This suggests that insufficiency of external pancreatic secretion was not complete in any of our 20 cases of chronic pancreatitis. Previous investigators<sup>8, 11-14</sup> have reported percentages of ingested nitrogen lost greater than those herein reported. The percentages ranged as high as 129.1 (table 4). In fact, in 9 of the 12 cases previously reported in which this percentage was determined, the percentage loss exceeded the highest percentage loss in the 20 cases of this series, and in 7 of the 12 cases previously reported the percentage loss exceeded the highest percentage loss in cases of total loss of pancreatic juice due to partial pancreatectomy and ligation of the pancreatic duct.

12. Calories lost in the stool have not been shown in tabular form. The average daily caloric content of the feces in patients without sequelae was not significantly different from that of the normal group, but in patients with sequelae the loss as fat and protein (nitrogen times 6.25) reached 536 calories per day, which is about six times the average loss of normal persons.

#### SUMMARY AND CONCLUSIONS

1. Intake-excretion studies have been conducted in 20 cases of chronic pancreatitis. In each case the patient ingested a diet containing 117.5 gm. of protein, 101.6 gm. of fat and 269.6 gm. of carbohydrate, and furnishing 2,463 calories per day.

In 10 cases, calcification, diabetes and grossly recognizable steatorrhea were not present, but in the remaining 10 cases, one or more of these diagnostically important sequelae of chronic pancreatitis was present to insure correct diagnosis without fecal analysis and to point to more advanced destruction of the pancreas than in the first 10 cases.

2. The difference between the average daily fecal values for total solids, fat and nitrogen for the normal group and for the group of patients without sequelae were not statistically significant but the differences between these values for the normal group and the group of patients with sequelae were statistically significant.

3. Fecal losses in the 20 cases varied over a wide range. The average daily total fecal solids varied from 8.5 to 87.6 gm. (normal limits 13.0 to 42.2 gm.), the average daily fecal fat from 3.1 to 44.1 gm. (normal limits 1.1 to 7.1 gm.) and the average daily fecal nitrogen 1.2 to 5.6 gm. (normal limits 0.9 to 2.5 gm.). In all cases the losses were less than occurred in those patients so far studied by us in which pancreatic juice was excluded completely from the intestine and the patient had ingested the same diet.

4. Fecal losses were roughly in proportion to pancreatic damage. Intake-

excretion studies showed insufficiency of external pancreatic secretion in all cases in which diabetes and calcification were present but in only 1 case in which these sequelae were absent.

5. Carefully conducted intake-excretion studies will demonstrate unsuspected insufficiency of external pancreatic secretion, and occasionally in the absence of other diagnostic features such studies will provide data diagnostic of chronic pancreatitis.

6. Analysis of the feces for total fat appears to give information of value in the early diagnosis of pancreatitis more frequently than does analysis for total fecal solids and fecal nitrogen.

7. Abnormal azotorrhea does not always accompany the abnormal steatorrhea of chronic pancreatitis. Abnormal steatorrhea apparently may precede the appearance of abnormal azotorrhea.

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## PANCREATIC FUNCTION AS MEASURED BY ANALYSIS OF DUODENAL CONTENTS BEFORE AND AFTER STIMULATION WITH SECRETIN\*†‡

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### INTRODUCTION

Investigators<sup>1-11</sup> using the secretin test generally agree that it is of value in detecting disease of the pancreas. However, the number of cases of pancreatitis to which the test has been applied remains small. Lagerlöf's<sup>7</sup> series of 11 cases of acute and 17 cases of chronic pancreatitis remains the largest. Diamond and Siegel<sup>2</sup> in 1940 studied 3 cases of pancreatitis and 3 cases of cyst of the pancreas, Hartwell<sup>5</sup> in 1941 studied 1 case of subsiding acute pancreatic necrosis, Pollard, Miller and Brewer<sup>9</sup> in 1942 studied 2 cases, Sjöberg<sup>11</sup> in 1944 studied 5 cases and Lake<sup>8</sup> in 1947 studied 2 cases of acute pancreatic necrosis and 5 cases of chronic pancreatitis. We are encouraged, therefore, to report our experience with the test in 28 cases of chronic pancreatitis and to present our evaluation of the test in the detection of external pancreatic function and in the diagnosis of pancreatitis.

### SUBJECTS STUDIED

The data on 20 normal subjects have been summarized in table 1. With 3 exceptions, the data were obtained from healthy young adults; however, these remaining 3 subjects did not have conditions affecting the pancreas.

The diagnosis of pancreatitis is not open to question in any of the 28 cases. In 16 of the 28 cases, the history of recurring attacks of abdominal pain, the presence of one or more of the three diagnostic sequelae of pancreatitis, namely, calcification, grossly fatty stools recognizable because of the bulky light-colored fatty appearance or because of the presence of free fat, and the finding at surgical exploration or necropsy (15 of 16 cases) of extensive disease of the pancreas, was convincing evidence of pancreatic disease. In the remaining

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12 cases, the recurring painful seizures, with features suggestive of pancreatitis, justified a presumptive diagnosis of pancreatitis. In 6 of 12 cases, the elevation of values for serum enzymes during painful seizures confirmed the diagnosis. In 9 of the 12 cases, surgical exploration at the Mayo Clinic, and in 3 of the 12, surgical exploration elsewhere, served to confirm the diagnosis in all 12 cases.

In all cases the secretin test was done in the interval between the acute seizures. In only 1 case (case 4) was elevation of enzymes, indicating activity of the process, present at the time the test was done. The test was repeated in 1 case only. In this case the results of the test were abnormal each time.

The cases have been grouped according to presence or absence of the sequelae of pancreatitis. In group 1 were placed 12 cases of pancreatitis without apparent sequelae and in group 2, 16 with these sequelae. Because of these sequelae and the surgical descriptions of the pancreas, it may be assumed that pancreatic destruction was more marked in group 2 than in group 1.

There were 22 males and 6 females. The age of onset fell in the first, third, fourth, fifth, sixth and seventh decades of life respectively in 2, 9, 6, 4, 5 and 2 cases. Other clinical features of cases of pancreatitis in this series were typical of the disease<sup>12</sup>.

#### PROCEDURE

After the subject had experienced a twelve hour fast, a dose of 1.5 grains (0.1 gm.) of pentobarbital sodium was given orally. One half hour later, a double lumen tube, described by Ågren and Lagerlöf<sup>1</sup>, was introduced into the stomach and the duodenum. The position of the tube was checked by roentgen examination in most cases. Continuous aspiration with a negative pressure of 20 to 30 mm. of mercury prevented the overflow of gastric juice into the duodenum and produced a continuous flow of duodenal contents. The duodenal contents were collected in two ten-minute periods before stimulation and in four ten-minute periods after stimulation. Purified secretin (Pancreotest, manufactured by Astra in Sweden) was given intravenously in doses of 1 clinical unit per kilogram of body weight.

#### LABORATORY METHODS

The volume was measured in cubic centimeters. The concentration of bicarbonate was determined by the use of the volumetric apparatus of Van Slyke. Amylase activity was determined by the method of Norby as modified by Ågren and Lagerlöf<sup>1</sup>. Determination of trypsin was carried out by the procedure described by Ågren and Lagerlöf<sup>1</sup>, which is the method outlined by Willstätter, Waldschmidt-Leitz, Dunaiturria and Küstner and modified by Christiansen. The activity of lipase was determined by the method of Cran-

dall and Cherry as modified by Comfort and Osterberg<sup>13</sup>. Total values for each ten minute period were obtained by multiplying the concentration by volume, and total values for the forty minute period were obtained by addition of the total values for the four ten-minute periods.

### RESULTS

*Analysis of the duodenal contents before stimulation with secretin.*—Data from analysis of duodenal contents collected during the first and second ten minute periods before the administration of secretin are not presented in detail. The results may be summarized by saying that average values for some of the determinations were lower for the groups of patients with pancreatitis than for normal persons, but that values for normal persons ranged so low that only when almost complete absence of bicarbonate and of the enzymes occurred did the data confirm the known existence of extensive parenchymatous destruction.

*Analysis of the duodenal contents after stimulation with secretin.* Volume.—Stimulation of pancreatic secretion in normal persons with secretin produces a prompt increase in average volume of fluid secreted. The average volume usually reaches a peak during the first ten minute period and thereafter declines. In patients with pancreatitis the average response is similar, but the peak of average volume is lower. It is lower in the group with, than in the group without, sequelae. The greater the damage to the acinar secreting cells the more likely it is that volumes will not rise but remain frozen at or near prestimulation levels. The volume of secretion tends to remain fixed at prestimulation levels in those cases in which great damage to the pancreas has occurred, as estimated by the duration and severity of the clinical manifestations of the disease, by the extensiveness of the calcification and by the severity of the diabetes and of the steatorrhea.

In group 1, which consisted of 12 patients who did not exhibit the sequelae, diabetes, calcification or gross steatorrhea, the mean total volume for all patients for the forty minutes after stimulation was 89.3 cc. (table 2). This figure is less than the mean volume of 122.5 cc. for the normal group (table 1), but the difference is not statistically significant. In 7 of the 12 cases, the volume was lower than the minimum obtained for normal persons. In 8 of the 12 cases the values for volume fell within the normal limits\*, but in the remaining 4 the values were more than two times the standard deviation below the normal mean and were, therefore, considered presumptively abnormal.

In group 2, which consisted of 16 patients who did exhibit one or more of the three sequelae, calcification, diabetes or gross steatorrhea, the mean total

\* The mean for normal persons  $\pm$  two times the standard deviation has been considered normal limits; values beyond those limits have been considered presumptively abnormal.

TABLE 1

Values for Average Concentration of Bicarbonate and for Total Volume, Bicarbonate, Amylase, Trypsin and Lipase in Normal Persons in the Forty Minute Sample after Stimulation with Secretin

	VOLUME	BICARBONATE		AMYLASE, GM. OF MALTOSE	TRYPSIN, CC. OF TENTH-NORMAL POTASSIUM HYDROXIDE	LIPASE, CC. OF TWENTIETH-NORMAL SODIUM HYDROXIDE
		Millimols per cubic centimeter	Millimols, total			
	cc.					
Cases...	20	12	12	20	20	19
Average*	122.5 ± 6.4	0.105 ± 0.004	14.8 ± 1.0	91.0 ± 9.6	117.7 ± 11.4	10,519 ± 1,335
Standard deviation...	28.7	0.014	3.5	43.0	49.4	5,820
Maximum..	192	0.128	17.75	266.0	208.0	20,760
Minimum...	90	0.072	10.70	29.0	79.0	539

\* The figure following the ± is the standard error of the mean.

TABLE 2

Values for Concentration of Bicarbonate and for Total Volume, Bicarbonate, Amylase, Trypsin and Lipase in 12 Patients with Chronic Relapsing Pancreatitis Without Sequelae for the Forty Minute Period Following Stimulation with Secretin (Group I)

CASE	VOLUME	BICARBONATE		AMYLASE, GM. OF MALTOSE	TRYPSIN, CC. OF TENTH-NORMAL POTASSIUM HYDROXIDE	LIPASE, CC. OF TWENTIETH-NORMAL SODIUM HYDROXIDE
		Millimols per cubic centimeter	Millimols, total			
	cc.					
1	158	0.088	14.2	54	165	6,858
2	150	0.088	13.8	113	145	22,471
3	140	0.086	11.6	114	148	8,920
4	116	0.089	10.3	14	153	16,466
5	101	0.098	9.9	135	112	16,084
6	87	0.065	5.7	56	95	14,662
7	81	0.063	4.8	131	71	2,416
8	66	0.078	5.0	57	44	3,316
9	58	0.077	3.9	56	60	7,790
10	41	0.063	2.4	10	52	5,671
11	41	0.068	2.3	36	29	5,119
12	33	0.038	1.3	25	24	956
Mean*....	89.3 ± 12.7	0.075 ± 0.005	7.1 ± 1.3	66.8 ± 13.0	91.5 ± 14.9	9,227 ± 1,936
Standard deviation...	44.0	0.017	4.6	45.1	51.7	6,712
Difference† from normal...	33.2 ± 13.3	0.030 ± 0.002	7.7 ± 1.7	24.2 ± 16.6	26.2 ± 19.0	1,292 ± 230

\* The figure following the ± is the standard error of the mean.

† Differences between the normal mean and the mean of this group.

volume was 53.3 cc. (table 3), which was less than half the mean total volume for the normal group (table 1). The difference between the two means (69.2 cc.) is statistically significant. In every one of the 16 cases, the volume was lower than the minimum (90 cc.) obtained for normal persons, but the value in only 9 of the 16 cases was presumptively abnormal.

Bicarbonate.—After stimulation with secretin, the average concentration of bicarbonate behaves in a fashion similar to that of average volume. It in-

TABLE 3

*Values for Concentration of Bicarbonate and for Total Volume, Bicarbonate, Amylase, Trypsin and Lipase in 16 Patients with Chronic Relapsing Pancreatitis with Sequelae for the Forty Minute Period Following Stimulation with Secretin (Group 2)*

CASE	VOLUME cc.	BICARBONATE		AMYLASE, GM. OF MALTOSE	TRYPSIN, CC. OF TENTH- NORMAL POTAS- SIUM HY- DROXIDE	LIPASE, CC. OF TWENTIETH- NORMAL SODIUM HYDROXIDE	SEQUELAE <sup>a</sup>		
		Millimols per cubic centimeter	Millimols, total				D	C	S
13	87	0.060	5.2	27	95	13,108	0	0	+
14	86	0.055	5.3	47	86	4,296	0	0	+
15	82	0.068	5.7	28	50	10,446	+	+	0
16	77	0.040	2.9	18	67	2,438	0	0	+
17	67	0.053	3.3	34	72	5,934	0	0	+
18	66	0.028	1.8	—	47	2,860	+	+	+
19	66	—	—	19	65	1,170	+	+	0
20	50†	0.051	2.9	11	30	4,865	+	0	+
21	49	0.078	3.1	38	56	3,505	+	0	0
22	48	0.035	1.7	0	51	3,000	+	+	+
23	47	0.015	0.7	2	14	2,344	0	+	+
24	35	0.022	0.8	6	30	1,277	+	+	+
25	32	0.027	0.9	24	26	1,878	+	0	0
26	32	0.045	1.4	4	29	2,910	+	+	0
27	16	0.030	0.5	8	7	620	0	+	0
28	13	0.015	1.3	1	20	143	0	+	+
Mean <sup>b</sup>	53.3 ± 5.9	0.042 ± 0.005	2.5 ± 0.5	17.8 ± 3.8	46.6 ± 6.5	3,800 ± 877			
Standard deviation	23.8	0.019	1.8	14.8	25.9	3,506			
Difference <sup>c</sup> from normal	69.2 ± 9.0	0.063 ± 0.002	12.3 ± 1.0	73.2 ± 12.0	71.1 ± 13.8	6,719 ± 164			

\* D = diabetes; C = calcification; S = gross steatorrhea recognized clinically; + = present; 0 = absent.

† Average of two tests.

‡ The figure following the ± is the standard error of the mean.

§ Differences between normal mean and mean of this group.

creases rapidly, but does not reach its peak until the second ten minute period and thereafter declines. In patients with pancreatitis, the average concentration of bicarbonate behaves in a similar fashion, but the peak of the average concentration is lower in the cases of pancreatitis than in normal persons. The peak is lower in cases of pancreatitis with sequelae than in cases of the disease without sequelae. The greater the damage to the pancreas, the lower the peak and the more likely it is that the concentration will remain fixed near the prestimulation level.

In group 1, the average mean concentration of bicarbonate for the forty minute period after stimulation was 0.075 millimols per cubic centimeter (table 2), a figure considerably below the figure of 0.105 millimols for normal groups (table 1). The difference between the means (0.030 millimols) is statistically significant. In 5 of the 12 cases, the value was lower than the lowest value obtained for normal persons. In the same 5 cases the average concentration of bicarbonate for the forty minute period was presumptively abnormal. In an additional 2 cases, the values, being about equal to the lower limit of normal, might be interpreted similarly in clinical practice.

In group 2, the average concentration of bicarbonate for the forty minute period was 0.042 millimols per cubic centimeter (table 3), a figure much less than the value of 0.105 millimols for normal persons (table 1). The difference between the two means (0.063 millimols per cubic centimeter) statistically is significant. In 14 of the 15 cases in which the concentration of bicarbonate was determined, the value was less than the minimal value obtained for normal persons. In the same 14 cases the average concentrations for bicarbonate were presumptively abnormal.

It is of interest to note that the highest concentrations attained during four ten-minute periods after stimulation in each of the 12 normal persons were respectively 0.150, 0.110, 0.140, 0.100, 0.150, 0.170, 0.110, 0.120, 0.140, 0.130, 0.126, and 0.132 millimols equivalent per cubic centimeter, that the highest concentration reached in those cases of group 1 in which the mean concentration for the forty minute period was presumptively abnormal was 0.098, and that the highest concentration in the cases of group 2 was 0.078 millimols per cubic centimeter, values that were lower than any of the corresponding values in normal persons. It appears that the diseased pancreas loses not only its ability for sustained secretion of bicarbonate, but also for attaining the high values reached by the normal pancreas.

The mean total bicarbonate for the forty minute period for the 12 cases of group 1 was 7.1 millimols per total sample (table 2). This value is much less than the corresponding value (14.8 millimols) for normal persons (table 1). The difference between the means (7.7 millimols) statistically is significant. In 9 of the 12 cases, the value was less than the minimal value obtained for normal persons. In 7 of the 12 cases, the value for total bicarbonate was presumptively abnormal.

The mean total bicarbonate for the 15 cases of group 2 in which bicarbonate was determined was 2.5 millimols per total sample (table 3), a value much below that (14.8 millimols) for normal persons (table 1). The difference between the two means (12.3 millimols) statistically is significant. In 15 of 15 cases the value for total bicarbonate was presumptively abnormal. Values for total bicarbonate were presumptively abnormal in those cases in which the peak concentration and average concentration of bicarbonate were low.

Enzymes.—In normal persons the average concentration of each enzyme is essentially the same in the first ten minute period as in the prestimulation period, but falls in the second ten minute period after stimulation and thereafter rises to normal. This behavior is less characteristic of lipase than of amylase and trypsin. In cases of pancreatitis the average concentrations tend to remain the same or to rise slightly above prestimulation values, but show a distinct tendency to be lower than in normal persons. This difference is more marked in cases of pancreatitis with sequelae than in those without sequelae. The fall in the second ten minute period is more marked in cases of pancreatitis without, than in those with, sequelae. In short, the average values in cases of pancreatitis with sequelae are lower in the prestimulation period, tend to remain at prestimulation levels in the first ten minute period and to fall little or none in the second ten minute period. Enzymes in general show a tendency to be fixed at low concentrations when the pancreas is badly diseased.

The concentrations of enzymes rarely disclose insufficiency of external pancreatic secretion. Thus, the mean concentration of trypsin for 20 normal persons during the second ten minute period after stimulation, when average concentrations reach their lowest values, was  $0.75 \pm 0.06$  cc., expressed in terms of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, and the normal limits, 0.23 to 1.27 cc. Thus, the value for concentration during this period must be very low or nil before it is presumptively abnormal. Actually, in only 2 of the 28 cases of pancreatitis studied did this value fall below 0.22 cc..

Because much emphasis has been placed on the values for total enzymes in the diagnosis of pancreatic disease, analysis of data pertaining to total enzymes per forty minute sample is of considerable interest. The mean value for total amylase for the cases of group 1 was 66.8 gm., expressed in terms of maltose per cubic centimeter of duodenal contents (table 2), a value somewhat less than the mean value (91.0 gm. of maltose) for the normal group (table 1). However, the difference between the two means is not significant. In 3 of the 12 cases, the value was lower than the minimal value (29 gm. of maltose) obtained for normal persons, but the values for total amylase in all cases fell within normal limits and were, therefore, presumptively normal. The mean value for total amylase for the 15 cases of group 2 in which amylase was determined was 17.8 gm. of maltose (table 3). This figure is much less than the mean value for total amylase for the normal group (91.0 gm. of maltose) (table 1), and obviously the difference between the two means is statistically significant. In 12 of the 15 cases, the value was less than the lowest value (29 gm. of maltose) obtained for normal persons, but in only 4 of the 12 cases were the values presumptively abnormal.

The mean value for total trypsin for the cases of group 1 was 91.5 cc. of tenth-normal potassium hydroxide (table 2). This value is somewhat lower

than that (117.7 cc.) for the normal group (table 1). The difference between the means (26.2 cc.) is not statistically significant. In 6 of the 12 cases, the value for total trypsin was less than the minimal value (79 cc.) obtained for normal persons, but the value in each of the 12 cases, falling within normal limits, was presumptively normal. The mean value for total trypsin for the cases of group 2 was 46.6 cc. of tenth-normal potassium hydroxide (table 3). This figure is much lower than the mean value for total trypsin for normal persons (117.7 cc.) (table 1), and the difference between the two means is significant. In 14 of the 16 cases, the value for total trypsin was less than the minimal value (79 cc.) obtained for normal persons, but in only 2 cases were the values presumptively abnormal.

The mean value for total lipase for the cases of group 1 (table 2) was 9,227 cc. of twentieth-normal sodium hydroxide, a value slightly below the mean for total lipase (10,519 cc.) in the normal group. In none of the 12 cases was the value lower than the lowest value obtained for normal persons (539 cc.) and the value in each of the 12 cases was presumptively normal. The mean value for total lipase in the cases of group 2 (table 3) was 3,800 cc. of twentieth-normal sodium hydroxide. This figure is much below the normal mean (10,519 cc.) (table 1) and the difference between the two means is statistically significant. In only 1 case was the value for total lipase lower than the minimal value (539 cc.) obtained for normal persons, and in all 16 cases, the values fell within normal limits.

The differences between the normal means and the means for group 1, for total amylase and trypsin were not significant, but they were significant for group 2. The differences between the normal means and the means for total lipase in both groups 1 and 2 were significant. Regardless of the significant differences in the means, values for total enzymes in the individual case rarely were presumptively abnormal.

#### SUMMARY AND DISCUSSION

Lagerlöf<sup>7</sup>; Pratt, Brugsch and Rostler<sup>10</sup>; Pollard, Miller and Brewer<sup>9</sup>, and Lake<sup>8</sup> recorded values for one hour after stimulation with secretin, and Diamond and Siegel<sup>2</sup> for sixty and eighty minutes. Because we have chosen to present data for the forty minute period after stimulation with secretin, comparison of our normal data with those of previous investigators has been possible only in a limited way. We have shortened the test in the interest of the patient and because the maximal effect of secretin is measured in the forty minute period after injection. We believe the results are equally as informative as those obtained from longer periods of study.

Werthessen<sup>14</sup> has analyzed data from the normal series of Ågren and Lagerlöf<sup>1</sup>; Diamond and Siegel<sup>2</sup>; Hartwell<sup>5</sup>, and Pratt, Brugsch and Rostler<sup>10</sup>. He

discarded the data of Pratt, Brugsch and Rostler because the secretin used was found subsequently to be 50 per cent below normal strength. In analysis of Hartwell's data he found that it would be necessary to pump for one hour without obtaining secretion to make a valid deduction on the basis of volume, and that a negative quantity of enzymes would have to be secreted in order for some of the determinations of enzymes to be considered significant. He was not able to combine for analysis the data regarding volume and enzymes from authors other than Hartwell, because standards were not interchangeable; however, because the values for bicarbonate were in basic units, he was able to combine and analyze the data of Ågren and Lagerlöf<sup>1</sup>, Diamond and Siegel<sup>2</sup>, and Hartwell<sup>3</sup> pertaining to concentration of bicarbonate. He found that that average values in the respective series were 0.115, 0.105 and 0.113 millimols per cubic centimeter and for the total group, 0.110 millimols per cubic centimeter. The similarity of the value for average concentration in the forty minute period for our normal series (0.105 millimols per cubic centimeter) is obvious.

The secretin test gives reliable information only when the strength of the secretin is standard and when the duodenal contents have been quantitatively aspirated, uncontaminated by acid gastric contents. Because, during the period when tests on patients with pancreatitis were being done, normal values were obtained in conditions such as duodenal ulcer and nontropical sprue, it seemed safe to assume that the strength of the secretin used was satisfactory. Great care in the technics of aspiration was exercised and data from those cases in which the technic was not good were discarded.

Statistical analysis of data from normal persons discloses that the variability of values for total enzymes is so large that a value in an individual case can be considered presumptively abnormal only if it is zero or very low. On the contrary, the ranges of values for volume, and for concentration of bicarbonate and total bicarbonate as disclosed by the standard deviation are relatively well defined at a level considerably above zero, and we cannot agree with Werthesen<sup>14</sup> that values for volume must be nil before they are significant. Lagerlöf's analysis of data from 48 normal persons disclosed similar trends. It is not surprising that values for volume and bicarbonate are of greater significance than values for enzymes, because pure secretin is an active stimulant of secretion of water and bicarbonate, and merely washes out the enzymes. It appears that active secretion of the enzymes is in response to stimulation of the vagus and to pancreozymin<sup>15, 16</sup>.

In 18 of the 28 cases, abnormal steatorrhea was not recognized clinically. In these 18 cases, abnormal external pancreatic function was not suspected. Presumptively abnormal values for total volume, average concentration of bicarbonate, total bicarbonate, amylase, trypsin and lipase were found, re-

spectively, in 8 of 18, 9 of 17, 12 of 17, 1 of 17, 1 of 18 and 0 of 18 cases in which these determinations were made. Presumptively abnormal values for volume and bicarbonate or for bicarbonate alone in 12 of the 18 cases disclosed unsuspected insufficiency of the external pancreatic secretion; those for enzymes, in only 2 cases.

In the remaining 10 of the 28 cases, abnormal steatorrhea was recognized clinically, and the existence of insufficiency of external secretion was at least strongly suspected before laboratory studies were made. Presumptively abnormal values for total volume, concentration of bicarbonate, total bicarbonate, amylase, trypsin and lipase were obtained respectively in 5, 10, 10, 3, 1, and 0 of the 10 cases. Presumptively abnormal values for volume and bicarbonate or for bicarbonate in 10 of 10 cases confirmed the clinical impression of existing pancreatic insufficiency, while the values for enzymes gave such an impression in only 3 cases. Determinations of volume, concentration of bicarbonate and total bicarbonate appear to be the part of the secretin test that is most informative of the state of external function of the pancreas. Determinations of total enzymes did not furnish information not given by determinations of volume and bicarbonate.

The secretin test furnished presumptively abnormal values for total volume, concentration of bicarbonate, total bicarbonate, total amylase, total trypsin and total lipase respectively in 4, 5, 7, 0, 0, 0, of the 12 cases of group 1 (table 2) in which the sequelæ, calcification, diabetes and gross steatorrhea were not demonstrable. Thus in 7 of 12 cases in which those diagnostically important sequelæ were not present to confirm the diagnosis of pancreatitis, presumptively abnormal values for volume and bicarbonate or for bicarbonate disclosed disturbance of external pancreatic secretion and furnished laboratory evidence of pancreatic disease which aided in diagnosis in the event the patients were seen only in intervals between attacks when serum enzyme values were normal. Determinations of total enzymes were of no assistance. In the remaining 16 cases (group 2, table 3) the diagnosis of chronic pancreatitis based upon the history and one or more of the three sequelæ, calcification, diabetes and gross steatorrhea, could not be questioned. Presumptively abnormal values for total volume, concentration of bicarbonate, total bicarbonate, total amylase, total trypsin and total lipase were found in this group respectively in 9 of 16, 14 of 15, 15 of 15, 4 of 15, 2 of 16 and 0 of 16 cases in which the factors were determined. Thus, determinations of total volume, of concentration of bicarbonate and of total bicarbonate furnished evidence of disturbance of external secretion and of pancreatic damage in every case of this group in which bicarbonate was determined, but in no case did determination of enzymes add to information obtained from determination of volume and bicarbonate. However, the secretin test was not necessary for diagnosis in these 16 cases in which the diagnostic sequelæ of pancreatitis were present.

These studies suggest that determination of enzymes might be deleted from the test without impairing its importance. In fact, the only good reason for retaining determination of enzymes, and in particular that of amylase, is to be found in the occasional case in which the value for amylase is low and the values for volume, bicarbonate and other enzymes are normal. This is the type 1 response of Lagerlöf. An example of this type of response is found in case 4 of group 1 (table 2). Such a response appears to be a reliable index of pancreatic disease but it has been observed too infrequently to judge finally of its value.

A rough correlation exists between the degree of destruction of the pancreas, as judged by the severity of the clinical course and the pathologic findings at operation or necropsy, and the result of the secretin test. In 4 cases (1, 2, 3 and 5) the response to secretin was within the normal range and the disease was relatively mild. In case 2 a single attack of pain had occurred one month before registration. This attack was preceded by intermittent mild epigastric bloating and distress of four years' duration. At exploration one month before admission the surgeon performed cholecystostomy and cholelithotomy and noted an inflammatory mass in the pancreas. In case 3 painful seizures up to ten days in duration had recurred every six months over a period of four years. At exploration two and one half years before admission an acute pancreatitis with necrosis had been found. In case 5 two acute seizures in a period of three months preceded the secretin test. The surgeon found a subacute pancreatitis, grade 2. In case 1 infrequent attacks over a period of eleven years preceded surgical discovery of an edematous pancreatitis nine months before the secretin test was given. In a fifth case (case 4), except for attacks of pain one and eight years after cholecystectomy performed fifteen years previously, the recurring seizures had been experienced during the nine months before admission. A mild jaundice and a slight elevation of the serum lipase indicated continued activity of the process, but the patient had been free of pain for ten days. Exploration revealed a stone in a stump of the gallbladder, a dilated common bile duct and chronic pancreatitis, grade 1, which was localized to the head of the pancreas. It was in this case that Lagerlöf's type 1 response was found. In another 7 cases (cases 6, 7, 8, 9, 10, 11 and 12) the response to secretin was subnormal and in all 7 cases surgical exploration at the clinic, or elsewhere, disclosed a diffusely diseased pancreas. In the remaining 16 of the 28 cases in which the sequelae of pancreatitis, namely, diabetes, calcification or steatorrhea together with the finding at operation of extensive destruction of the parenchymal structures, the results of the secretin test were, on the average, more abnormal than in the preceding 7 cases.

In 14 cases of this series, analysis of feces for total solids, fat and nitrogen, as well as analysis of the duodenal contents after stimulation with secretin, has been performed. Comparison of the results obtained by these two methods

of detecting disturbance of the external function appears to indicate that the secretin test is the more sensitive test of abnormal external function. In 3 cases, neither fecal analysis nor the secretin test indicated insufficiency of external pancreatic secretion. In 4 cases, fecal analysis did not, but the secretin test did, disclose impairment of function. In another 3 cases in which the values for total fecal fat were presumptively abnormal, but just above the upper limits of normal (fecal nitrogen values were normal), the secretin test disclosed definite impairment. Finally, in 4 cases, both fecal analysis and the secretin test showed definite impairment of external function. In each of the 4 cases gross steatorrhea was present clinically. In short, in 7 of the 14 cases the results of the two tests were in agreement. In 4 cases the secretin test demonstrated impairment of external secretion when fecal analysis did not, and in another 3 cases the secretin test perhaps gave more definite evidence than did fecal analysis. The secretin test disclosed insufficiency of external secretion more often and appears to be of greater value in the diagnosis of chronic pancreatitis than does fecal analysis.

In practice, the diagnosis of pancreatitis is not based upon the secretin test alone; it is based upon clinical and laboratory data other than the secretin test. The secretin test alone will not distinguish between impaired external function due to pancreatitis and that due to other causes. The frequency with which the secretin test will aid in the diagnosis of pancreatitis and its ultimate value will be determined by the frequency with which it is applied to cases of pancreatitis without diagnostic sequelae, seen only in the interval between seizures when values for serum enzymes are not elevated.

#### CONCLUSIONS

The duodenal contents in 28 cases of proved chronic pancreatitis have been analyzed for volume, bicarbonate and enzyme content before and after stimulation with secretin.

Analysis of duodenal contents before stimulation with secretin disclosed disturbance of external function only when parenchymatous damage was extreme and then very rarely.

The values for volume of duodenal contents, for concentration of bicarbonate and for total bicarbonate for the forty minute period after stimulation disclosed insufficiency of external pancreatic secretion in all cases of pancreatitis with extensive destruction of the parenchymal structures as indicated by the presence of calcification, diabetes and steatorrhea. The same analyses of the duodenal contents in cases of chronic pancreatitis without these evidences of extensive damage disclosed disturbance of external function in more than half of the cases studied. Analysis of the duodenal contents for total enzymes secreted in the forty minute period after injection of secretin disclosed disturbance

of external function only in a few cases of pancreatitis, usually in those with marked destruction of the parenchyma.

Determinations of values for total volume, concentration of bicarbonate and total bicarbonate are the important part of the secretin test. It appears from this study that the test could be simplified, without detracting seriously from its value, by limiting the determinations to those of volume, concentration of bicarbonate and of total bicarbonate and by shortening the period of collection of duodenal contents to forty minutes after stimulation with secretin.

Values for volume, for concentration of bicarbonate and for total bicarbonate following administration of secretin gave evidence of insufficiency of external function and were of diagnostic importance in cases in which the diagnostic sequelae of pancreatitis were not present. Also, such values gave evidence of insufficiency of external function when stool analysis did not.

The secretin test has a definite but limited place in the diagnosis of pancreatitis.

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## STUDIES IN PANCREATIC FUNCTION

### I. PRELIMINARY SERIES OF CLINICAL STUDIES WITH THE SECRETIN TEST\*

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In 1902 Bayliss and Starling<sup>1</sup> showed that the flow of pancreatic juice and bile was stimulated by a hormone, secretin, which is produced by the action of acid and chyme on the duodenal mucosa. The use of this hormone for the study of external pancreatic secretion was initiated in France by Chiray and his coworkers<sup>2</sup>. In 1934 Voegtlin, Greengard, and Ivy<sup>3</sup> conducted an extensive investigation of both the human and the canine response to secretin, using a duodenal extract prepared in their laboratory. The early studies were hampered by the impurity of the secretin extracts and the difficulty in obtaining uncontaminated duodenal juice quantitatively. These obstacles were subsequently overcome by Hammersten who produced a nontoxic, cholecystokinin-free secretin; and by his pupils, Ågren and Lagerlöf, who drained the duodenum by means of a double-lumen gastroduodenal tube under constant suction. The extensive studies of these Swedish investigators<sup>4, 5, 6, 7, 8, 9</sup>, later confirmed in America by the work of Diamond<sup>10, 11, 12</sup> and others<sup>13</sup>, established the characteristics of the normal secretin response and the clinical significance of this response as a test in pancreatic disease.

The present study was started almost 2 years ago to investigate pancreatic function, not only in suspected pancreatic disorders, but also, in such disease groups as obstructive jaundice, hepatitis, postcholecystectomy syndrome, and ulcerative colitis—with a view to the addition of the secretin pancreatic test to the diagnostic armamentarium of the Hospital. This report deals with the findings in 145 cases.

#### PROCEDURE

The tests were all performed with the patient in the fasting state. Under fluoroscopic control, a Diamond radio-opaque double-lumen gastro-duodenal tube† was placed in the duodenal loop. The tip of this particular tube was always positioned at the ligament of Treitz, as illustrated in Fig. 1. Both gastric and duodenal outlets were maintained under constant suction by means of a Gomco electric pump. After the duodenal aspirate had become crystal

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‡ Manufactured by Davol Rubber Company, Providence, R.I.

clear and alkaline, the drainage fluid was collected for a control period of 20 minutes. Following this, 1 clinical unit of secretin/kg. body weight, the standard submaximal pancreatic stimulus used by Lagerlöf<sup>8</sup>, was injected intravenously. Because of difficulties encountered in obtaining secretin at the time of this work, it was necessary to use preparations of different sources and ages, i.e., Astra (1938, 1944, 1945, 1946) and Wyeth (1946, 1948). Lager-

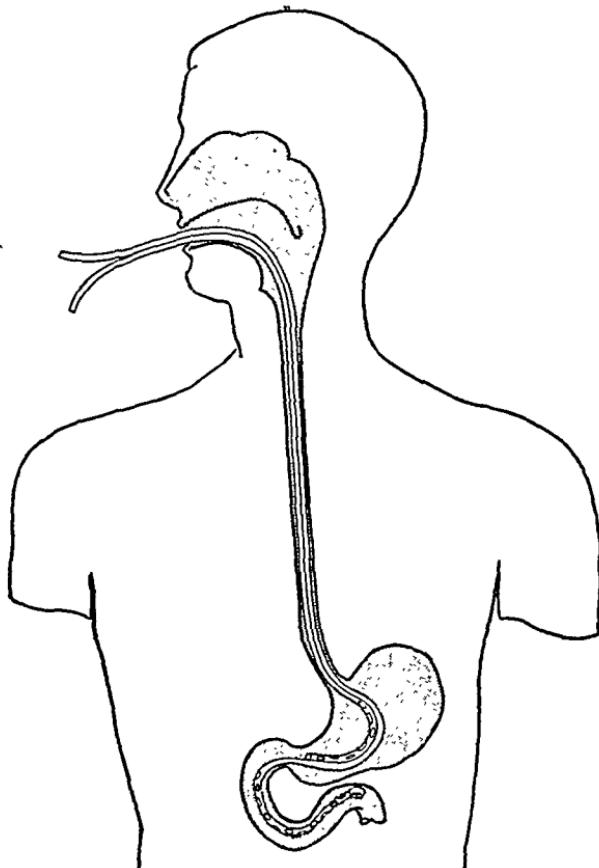


FIG. 1. POSITION OF THE GASTRO-DUODENAL TUBE FOR THE SECRETIN TEST

löf has shown that the Astra preparations undergo a slow constant deterioration, a fact which will be referred to in the subsequent analysis of the data.

Following the administration of secretin, simultaneous gastric and duodenal specimens were collected during four successive 20-minute periods. Eighty minutes is a longer collection period than advocated by some investigators<sup>14, 15, 18</sup>, but it was chosen to make the results comparable to those obtained by Lagerlöf and Diamond. Furthermore, it was felt that a total col-

lection time corresponding to the duration of the entire response to a dosage of 1 unit/kg.—about 80 minutes<sup>3, 5, 7, 9, 10, 13</sup>—would offer a more rigorous procedure.

The gastric specimens were examined for the following:

	<i>Method</i>	<i>Expressed as</i>
1. Volume		cc.
2. Acidity	glass electrode	pH
3. Bile pigment	colorimeter ( $K_2Cr_2O_7$ stand.)	icterus index
4. Blood	guaiac test	$\pm$

This was done as a measure of duodenal regurgitation. When the latter occurred, there was a sudden increase in volume, a rise in pH, and the appearance of bile in the gastric specimen. Duodenal regurgitation was never persistent enough nor of sufficient (estimated) magnitude to invalidate the clinical significance of the test.

The following determinations were made on the duodenal fractions:

	<i>Method</i>	<i>Expressed as</i>
1. Volume (single and combined specimens)		cc. and cc./kg.
2. pH	glass electrode	pH
3. Bicarbonate concentration	Van Slyke (volumetric)	meq./L.
4. Bile pigment	colorimeter ( $K_2Cr_2O_7$ stand.)	icterus index
5. Blood	guaiac test	$\pm$
6. Amylase concentration (combined specimens)	modified Somogyi method	units/cc. and units/kg.

Previous workers have stated that volume response, maximum bicarbonate concentration, and total quantity of amylase produced are the three most significant characteristics of the pancreatic secretion stimulated by secretin. The pH values were determined as an indication of gastric contamination of the duodenal specimens. Whenever the pH drops below 7.0, low bicarbonate and enzyme values result from neutralization and inactivation respectively. In the present study, only three tests had to be repeated because of such gastric contamination. The behavior of biliary pigment concentrations during the secretin test seemed to merit further study, particularly in relation to its use for differential diagnosis in biliary tract disease. Whether the omission of trypsin and lipase determinations is justifiable, as Lagerlöf<sup>9</sup> stated, or whether dissociated enzyme deficiencies exist, as Diamond<sup>12</sup> and others<sup>16</sup> have reported, only further investigation with improved chemical methods can demonstrate.

#### SERIES OF "NORMAL" TESTS

The normal series consists of 93 tests on patients in whom pancreatic disease was not suspected clinically or was excluded at laparotomy (Table I).

TABLE I  
*Secretin response data*  
 Normal series

TEST NO.	TOTAL VOLUME	MAX. BICARB.	COMBINED AMYLASE		TEST NO.	TOTAL VOLUME	MAX. BICARB.	COMBINED AMYLASE	
			cc./kg.	meq./L.				u./cc.	u./kg.
2	2.1	93	2.6	5.5	74	3.1	110	8.7	27.0
11	3.7	92	5.6	20.5	75	3.2	99	6.8	21.8
12	3.8	78	3.8	14.1	78	2.7	89	5.4	14.6
13	3.8	115	2.8	10.6	79	4.1	121	4.4	18.0
14	4.7	92	4.8	22.4	80	2.5	103	5.9	14.3
15	2.1	111	5.4	11.4	83	2.2	97	5.5	14.5
21	4.9	101	3.7	18.2	84	3.3	100	8.8	29.0
22	2.4	99	5.7	13.8	85	2.9	63	3.6	10.4
23	3.4	92	3.3	11.3	87	2.8	111	7.2	20.2
25	4.8	101	6.4	30.7	88	2.2	110	5.4	20.0
27	3.4	105	2.0	6.8	89	1.7	113	20.0	30.4
29	5.3	60	1.8	9.4	90	3.7	101	5.4	20.0
30	2.6	103	5.0	13.0	91	5.5	93	4.4	34.2
31	4.0	85	2.6	10.3	93	3.4	90	4.3	14.6
32	7.5	70	4.0	30.0	94	5.5	113	7.5	41.3
33	5.6	111	5.0	28.4	96	2.1	114	9.8	20.6
34	2.2	104	9.5	21.2	97	2.5	106	2.4	6.0
35	3.1	115	8.1	25.2	98	2.0	90	5.4	10.8
37	4.1	104	1.6	6.7	99	2.3	108	3.6	8.3
38	2.3	89	8.8	19.7	100	2.3	133	9.8	22.5
41	2.4	78	3.0	7.4	102	1.9	106	3.2	6.1
42	3.9	93	2.9	11.5	103	3.8	105	7.5	28.5
44	3.9	72	2.0	11.3	104	3.4	112	2.8	9.5
47	2.9	107	8.3	23.8	105	3.2	100	3.4	10.9
48	3.1	113	9.5	29.0	106	3.2	92	3.4	10.9
49	2.6	100	4.5	10.5	107	3.6	125	9.2	33.0
51	3.8	99	4.1	15.6	108	2.4	89	2.7	6.5
52	4.5	103	2.8	12.3	109	3.6	128	4.9	17.6
53	2.6	112	9.9	25.9	110	2.2	126	3.6	7.9
54	6.4	90	1.0	6.6	112	4.5	114	6.1	27.5
55	2.6	126	4.5	11.7	113	2.6	106	6.1	15.9
56	3.9	120	5.5	21.4	114	3.2	109	4.1	13.1
57	5.0	119	4.5	22.3	115	2.6	106	9.7	34.9
58	4.3	116	4.5	19.4	116	2.3	114	2.8	6.4
59	6.0	133	1.1	6.5	117	3.4	92	5.9	20.6
60	5.2	92	2.8	14.4	120	3.0	114	2.8	6.4
61	4.4	108	4.6	20.2	121	2.2	113	6.1	13.4
62	6.0	106	5.8	34.0	124	3.1	71	3.3	10.2
63	3.4	134	6.6	22.4	126	2.8	114	4.7	13.1
64	2.1	129	4.9	10.3	127	3.7	117	5.3	19.5
65	4.7	81	2.4	11.4	128	3.8	89	3.1	11.7
66	6.0	92	3.7	24.6	132	2.8	108	5.8	16.2
67	4.5	90	6.4	28.9	133	2.8	98	7.5	21.0
68	5.6	112	3.0	16.8	134	3.1	137	3.1	9.6
71	2.7	133	7.3	19.7	136	4.4	103	7.7	33.8
137	2.0	89	3.5	7.0	138	2.7	118	8.6	23.2

The data from this group of patients have been compared statistically with those of similar series (Table II) reported by Lagerlöf<sup>9</sup>, Diamond<sup>11</sup>, and Lake<sup>18</sup>. The mean bicarbonate values are in good agreement, for all four series. The average volumes, also, are reasonably concordant except for those in Diamond's series which are lower. The mean amylase quantities, however, show widespread deviation from group to group. The scatter of the data (as measured by the coefficient of variation,  $V_c$ ) follows a pattern similar to that of the means,

TABLE II  
*Statistical comparison of "normal" secretin response data from various sources*

	NO. OF CASES	TIME	TOTAL VOLUME		MAXIMUM BICARD. CONC.	AMYLASE			
			cc.	cc./kg.		Conc.	Quantity		
							u./cc.	total u.	
Present series	93	min. 80	99-449	1.7-7.5	60-134	1.0-20.0	318-2551	5.5-41.3	
Range			205±7	3.5±0.1	104±2	5.3±0.3	1033±53	17.4±0.9	
Mean			69	1.1	16	2.7	507	8.2	
$\sigma$			33.7%	31.4%	15.3%	50.9%	49.1%	47.1%	
$V_c$			7	0.1	1	0.3	53	0.8	
Diamond	24	80	66-277	1.0-3.7	50-128		243-1156	3.8-18.8	
Range			169	2.6	106		609	9.4	
Mean			51	0.7	17		233	3.7	
$\sigma$			30.2%	26.9%	16.0%		38.3%	39.4%	
$V_c$			10	0.1	3		48	0.8	
Lake	18	60	94-345	1.3-5.8	76-134	0.7-4.2	222-798	3.1-14.2	
Range			186	3.4	104	2.2	394	7.4	
Mean			59	1.3	18	0.8	160	3.4	
$\sigma$			31.7%	38.2%	17.3%	36.4%	40.6%	45.9%	
$V_c$			14	0.3	4	0.02	39	0.8	
Lagerlöf	33	80	104-266	2.2-5.5	94-137		400-1130	6.8-15.7	
Range			203±4	3.8±.2	115±3		637±38	12.6±0.9	
Mean			29	0.7	11		200	3.4	
$\sigma$			14.3%	18.4%	9.6%		31.4%	27.0%	
$V_c$			5	0.1	2		35	0.6	

i.e., least variability for bicarbonate and greatest for the enzyme. The high scatter of the amylase data, both within each series and across all four, is a logical consequence of several factors: (1) Whereas the content of the enzyme-stimulating hormone, pancreozymin, is probably highly variable in different preparations, the content of the fluid- and bicarbonate-stimulating hormone, secretin, is standardized. (2) Variations in duodenal pH just before the secretin injection and in vagal tone during the aspirations, must not be overlooked as influencing irregularly the rate of enzyme secretion.

The units used for evaluation of the data, and the ranges of values adopted as norms in these preliminary studies, were essentially those of Lagerlöf: i.e., total volume—2.0 cc. or more/kg/80 minutes, maximum bicarbonate concentration—90 meq. or more/liter, and amylase quantity—6.0 units or more/kg/80 minutes. These criteria were employed in preference to any derived from the present series of "normals" because five different secretin preparations had been used in the tests.

Lagerlöf<sup>9</sup> has pointed out that the secretin potency deteriorates at a fixed rate. Hence, in comparing results obtained with preparations of different ages, he made an adjustment for this deterioration. This was not feasible in the present study because the limited supply of secretin prevented the necessary comparative standardizations. Now, that a standard preparation of secretin has become available in this country, it is important that a new set of criteria of normalcy be set up, based on rigorous statistical considerations. Until this has been done, however, small isolated deviations from the present norms cannot be accepted as clear-cut evidence of pancreatic dysfunction. Therefore, values which are slightly less than the lower limit of "normalcy" (deviations less than 10%) are accepted here as indicating abnormal pancreatic response only when at least 2 of the 3 factors manifest such a depression. Single large deviations (deviations greater than 10%), on the other hand, are taken as being significant.

#### ABNORMAL MATERIAL

The abnormal material is presented as four disease groups: pancreatic carcinoma, pancreatitis, post-cholecystectomy syndrome, and jaundice.

##### *Pancreatic Carcinoma*

Sixteen cases of suspected and subsequently surgically proved pancreatic carcinomas were studied (Table III). Fifteen patients (with tumors of the head or body or both) showed abnormal responses to secretin: in 12 instances the total amylase production was depressed, in 10 the volume was low; only in 5 was the amylase concentration subnormal, and in 3 was the bicarbonate concentration markedly reduced. The one patient with normal findings had an ulcerating carcinoma of the papilla of Vater which did not produce either pancreatic or common duct obstruction. Normal secretin findings have been reported in tumors of the pancreatic tail as well by Lake<sup>18</sup> and others<sup>16</sup>. Three tests were done on patients with carcinomas contiguous to the pancreas but not involving the pancreatic ducts (Table IV). The secretin responses were normal in all three. Thus the alteration of secretion in pancreatic malignancy appears to depend primarily upon the site and severity of pancreatic duct obstruction. Volume and factors dependent upon it (e.g., quantity of amylase)

show greater changes than do the concentration values, which may be entirely normal. This dissociation of response is in accordance with the underlying physiological pathology—the primary disturbance being ductal obstruction with consequent diminution of the volume of secretion which enters the duo-

TABLE III  
*Pancreatic carcinoma*

NAME	TOTAL VOLUME	MAX. BICARB CONC.	AMYLASE		LOCATION*
			Conc.	Total	
F. K.	1.1	90	1.0	1.1	B and H
N. M.	1.6	95	2.5	4.0	B
R. E.	2.0	78	2.0	4.0	H
L. C.	1.8	84	1.1	1.9	B
M. A.	1.9	69	4.8	9.1	H
B. Y.	1.9	99	1.7	3.3	B
B. P.	1.0	54	3.8	3.8	B
J. M.	1.0	104	3.7	3.7	P
J. N.	1.4	99	9.1	12.7	H
P. C.	1.4	70	3.7	5.2	B and H
B. D.	1.1	38	4.1	4.5	H
A. H.	3.2	92	3.4	10.9	P
A. C.	0.5	44	0.9	0.4	H
E. G.	1.9	31	0.5	0.9	H
J. L.	1.0	24	0.2	0.2	B and H
B. G.	1.2	100	4.5	5.3	H
Mean.....	1.5	73	2.9	4.4	
Norm.....	3.5	104	5.3	17.4	

\* B = body; H = head; and P = papilla of Vater.

TABLE IV  
*Malignancies contiguous to pancreas*  
Secretin response data

NAME	TOTAL VOL.	MAX. BICARB. CONC.	TOTAL AMYLASE	LOCATION			
				cc./kg.	meq./L.	u./kg.	
M. M.	7.5	70	30.0				1° Ca duodenum
C. F.	3.1	113	29.0				Retroperitoneal Sa
L. O.	1.9	113	30.4				Ca commonduct

denum; secondarily, there may be parenchymal cell damage leading to a lowering in concentration of bicarbonate and enzyme.

#### *Acute and Chronic Pancreatitis*

Eight cases of acute non-fatal pancreatitis were studied with secretin during the first few weeks after the onset of symptoms, and 3 additional patients were

tested after recovery from a single attack (Table V). Two of the acute cases, both tested within the first week of illness (5th and 7th day respectively), exhibited normal secretin responses. One of these (E.H.), upon exploration following the secretin test, had fat necrosis; the second (A.L.) recovered spontaneously. The other 6 acute cases all had abnormally low amylase with volumes, more or less depressed. The bicarbonate concentrations in all 8 cases of acute pancreatitis were essentially normal. The two tests performed on asymptomatic patients 1 and 25 years after exploration for acute pancreatitis, and the one done on a patient 3 months after drainage of a pancreatic abscess, yielded normal findings.

TABLE V  
*Acute pancreatitis*  
Secretin response data (11 cases)

NAME	TOTAL VOL	MAX. BICARB. CONC	DUODENAL AMYLASE		BLOOD AMYLASE	PERIOD AFTER ONSET	OPERATIVE FINDINGS
			Conc.	Total			
T. Z.	2.1	79	0.9	1.8	85	1 day	Subacute Pancreatitis
A. L.	3.9	82	2.2	8.6	512-144	5 days	
M. C.	0.7	96	5.6	4.1	500	13 days	Fat necrosis
	2.6	75	5.1	13.3	320	40 days	
I. S.	2.9	68	0.04	1.3	140	15 days	Acute Pancreatitis
J. B.	1.1	111	0.7	0.8	1000-125	1 week	
E. H.	2.8	99	5.0	14.0	340-63	1 week	Fat necrosis
W. J.	1.1	106	7.2	7.2	333	3 weeks	Ac. hemmor. Pancreatitis
C. M.	1.6	109	2.0	3.2	664-67	3 weeks	Subacute Pancreatitis
D. H.	2.0	91	4.4	8.8	109	3 months	Panc. Abscess
M. Z.	3.1	88	6.2	18.9	180	1 year	Fat necrosis
T. B.	2.5	106	2.4	6.0	50	25 years	Fat necrosis

These results are in agreement with Lagerlöf's observations in 14 patients upon whom the studies were performed on the 6-14th day of illness. In his severe cases there was a reduction of volume, bicarbonate, and amylase; in the milder ones, only a dissociated depression of the enzyme. Hence, he concluded that enzyme production is the first factor to be disturbed in pancreatitis.

The findings in these cases of mild acute pancreatitis confirm the view that disturbance in function is temporary and that recovery takes place with surprising rapidity. Therefore, further study during the first few days of illness is needed to demonstrate how quickly reversal may take place. Certainly, it is clear, that at the end of the first week of symptoms, a normal secretin response does not exclude acute pancreatic inflammation. On the other hand, in some instances the pathological changes are irreversible and culminate in a progressive destruction of the parenchyma. Such patients have persistent symptoms and are better classified as chronic relapsing pancreatitis. Here,

the secretin response may be expected to remain abnormal for a long time, if not permanently.

This was found to be so in the 7 cases of chronic relapsing pancreatitis which were studied (Table VI). In all the tests there is marked depression of the responses to secretin: the bicarbonate concentration shows the greatest and most consistent lowering; amylase and volume are relatively less affected.

Such consistent marked depression of pancreatic secretion in chronic pancreatitis has not always been observed by other investigators. Lake's<sup>18</sup> recent report reviews 5 cases in which the abnormalities are slight. In 1936, Ågren and Lagerlöf<sup>6</sup> reported normal secretin findings in 9 out of 10 cases of "suspected" chronic pancreatitis. However, a subsequent study of 13 cases, published in 1942 by Lagerlöf<sup>9</sup>, yielded abnormal findings in every instance; 9 of

TABLE VI  
*Chronic pancreatitis*  
Secretin response data (7 cases)

NAME	TOTAL VOL. cc./kg.	MAX. BICARB. CONC. meg./L.	AMYLASE		BLOOD AMYLASE mg. %	LESION
			Conc. u./cc.	Total u./kg.		
C. N.	0.8	59	0.4	0.3	119	Calcinosis
S. G.	2.2	28	0.8	1.9	190	Pseudocysts
	2.1	50	5.3	10.8	85	Ac. Hem. Pancreatitis
B. R.	1.3	29	0.2	0.3	180	Calcinosis
N. G.	2.7	59	0.8	2.2	55	Chr. Pancreatitis
	1.2	23	0.02	0.02		
S. C.	1.2	25	3.1	3.8	71	Chr. Pancreatitis
R. F.	2.5	53	2.1	5.3	110	Pancreatic Cyst
J. B.	1.2	48	3.3	3.9	60	Calcinosis

these were proved by biopsy. Such inconsistencies are due to a lack of rigid diagnostic criteria. In the present series, no patient was accepted as having chronic pancreatitis on the basis of history alone, nor merely as the result of an operative description of enlargement or firmness of the pancreas. Only those cases were included which presented either radiographic pancreatic calcification, or persistent symptoms supported by biopsy evidence. It is possible that such rigid restriction results in the selection of only the more severe cases, but a relaxation of diagnostic standards would have led to the inclusion of many cases which are not pancreatitis.

#### *Post-Cholecystectomy Syndrome*

Twenty tests were done on patients who had persistent, unaccounted for, digestive complaints following cholecystectomy—so-called post-cholecystec-

tomy syndrome (Table VII). Only one patient had an abnormal secretin response—due, as subsequently revealed by exploration, to metastatic pancreatic carcinoma. In no other case did the pancreatostest give any evidence that pancreatic disease was the cause of the symptoms.

The behavior of the biliary pigment concentration during the secretin test is a collateral study of considerable clinical significance in this particular group.

TABLE VII  
*Post-cholecystectomy syndrome*  
Secretin Response Data (20 cases)

NAME	PANCREATIC SECRETION				ICT. IND. CURVE (TYPE)	Inter- pretation	OPERATIVE FINDINGS
	Total Vol. cc./kg.	Max. Bicarb. Conc. meg./L.	Total Amyl- ase u./kg.	Inter- pretation			
F. F.	4.9	101	18.2	N	C	obst.	
M. G.	3.4	92	11.3	N	B	N	
B. Y.	1.9	99	3.3	Abn.	B	N	Ca of pancreas
J. S.	4.0	85	10.3	N	B	N	
J. L.	4.1	104	6.7	N	B	N	Gastric ulcer
B. G.	3.9	93	11.5	N	B	N	
S. B.	4.5	103	12.3	N	B	N	
E. P.	2.6	126	11.7	N	B	obst.	
M. Y.	5.0	119	22.3	N	B	N	
S. S.	6.0	133	6.5	N	C	obst.	Excision
E. M.	4.7	81	11.4	N	B	N	Stricture CD
B. S.	2.5	103	14.3	N	B	N	Biliary cirrhosis
S. H.	2.8	111	20.2	N	B	N	
S. G.	2.0	90	10.8	N	B	N	
M. S.	2.4	89	6.5	N	B	N	
J. F.	3.4	92	20.6	N	B	N	CD Normal
N. R.	3.7	117	19.5	N	B	N	CD Normal
J. A.	4.4	103	33.8	N	B	N	
D. B.	2.0	89	7.0	N	B	N	
A. J.	3.6	104	16.6	N	B	N	

N = Normal.

For this purpose, the icterus index of successive duodenal specimens is plotted against the time of aspiration. Ågren<sup>19</sup>, Diamond<sup>20</sup>, and Lake<sup>18</sup> reported good correlation between the biliary pigment curve and the functioning state of the gall bladder. In their studies patients could be classified according to 3 types of curve. In those with a normally functioning gall bladder, the icterus index falls during the test from its initial value to almost complete disappearance of bile, and then rises again (fig. 2, curve type A). In patients with no gall bladder function (due to biliary disease or cholecystectomy) the initial icterus

index is usually higher than in normals and all the specimens remain heavily bile-tinged throughout the test. Nevertheless, this curve (type B) also shows a depression, but the icterus index never reaches a value lower than 5. Complete biliary obstruction, of course, is reflected in the absence of bile pigment in the duodenal drainage (type D). The physiological interpretation of these responses is as follows: In the normal patient bile from the liver enters the gall bladder and is discharged into the duodenum intermittently, whereas in patients with no gall bladder function bile must, for lack of a reservoir, enter the duodenum continuously. As a result (during the period of maximum pancreatic flow) in the presence of a functioning gall bladder there is marked dilution of bile in the duodenal specimens, whereas in its absence, there is only a very slight dilution.

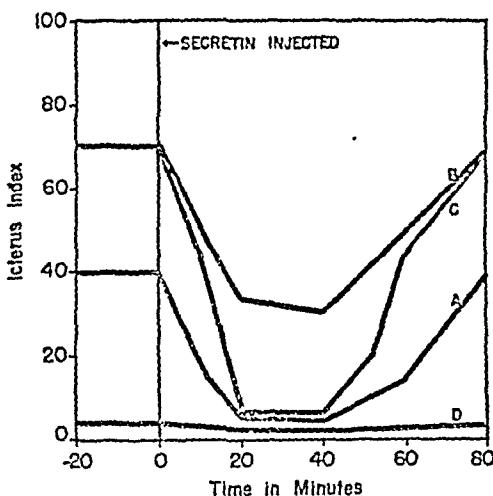


FIG. 2. DUODENAL ICTERUS INDEX CURVES FOLLOWING INTRAVENOUS SECRETIN

In the post-cholecystectomy syndrome group the biliary pigment curve might be expected to belong to type B—that is, all the drainage specimens should be strongly colored with bile. Three patients in this series, however, presented a curve resembling type A—except that the pre-secretin and terminal levels were higher (type C). In other words, during the period of maximum pancreatic flow, the duodenal drainage was colorless or almost so. Thus, these patients acted as if they had a gall bladder or other biliary reservoir, a behavior which suggests at once common duct dilatation due to some form of incomplete obstruction. One of these 3 patients (S.S.) was explored on the basis of this assumption and the prediction confirmed. The type C icterus index curve was also encountered in 5 other cholecystectomized cases which are not included in the preceding group because of presence of jaundice at some time in the clinical course. At laparotomy, the diagnosis of incomplete obstruction and dilatation of the common duct was corroborated in all 5 cases,

the several causes of obstruction being choledocholithiasis, postoperative strictures, and idiopathic stenosis of the papilla of Vater.

Thus the secretin test is of great value in the investigation of post-cholecystectomy syndrome cases. It may make possible not only the exclusion of pancreatic disease but also it may reveal disease in the biliary tract.

### *Jaundice*

Thirty-seven cases with jaundice were also studied. Ten of these patients had hepatitis (Table VIII), and were investigated to determine whether there was any characteristic change in pancreatic secretion or in the biliary pigment response. In Diamond's review<sup>11</sup>, 2 of 5 cases of toxic hepatitis showed low enzyme response. Lake<sup>18</sup> reports no abnormalities in 5 comparable patients.

TABLE VIII  
*Hepatitis*  
Secretin response data (10 cases)

NAME	TOTAL VOL. cc./kg.	MAX. BICARB. meq./L.	TOTAL AMYLASE u./kg.	PANC. FUNCTION	ICT. IND. CURVE
F. T.	3.4	105	6.8	Normal	A
J. S.	2.6	103	13.0	Normal	A
L. R.	5.3	60	9.4	Normal	A
M. S.	5.2	92	14.4	Normal	D
J. K.	6.0	92	24.6	Normal	A
E. P.	3.7	101	20.0	Normal	B
A. S.	3.2	100	10.9	Normal	A
L. G.	4.5	114	27.5	Normal	B
G. T.	3.2	109	13.1	Normal	A
D. P.	3.1	71	10.2	Normal	A

The findings in the present series are in agreement with those of the latter investigator; all 10 patients had normal pancreatic secretion.

The biliary pigment curves fell into categories A, B, and D—functioning gall bladder, non-functioning gall bladder, and biliary obstruction. The type of response is roughly correlated with the phase of the pathological process: early stage—obstructive (D), early recovery stage—hypercholeresis (B), and late recovery stage—normal biliary flow (A). It is apparent, therefore, that the secretin test is of no value in the differential diagnosis between hepatitis and extrahepatic biliary tract obstructive jaundice. On the other hand it may be of assistance when the choice lies between hepatitis and obstructive jaundice due to pancreatic malignancy.

Twenty-seven patients with obstructive jaundice were tested with secretin (Table IX). Among these there were 10 instances of abnormal pancreatic

TABLE IX  
*Obstructive jaundice*  
Secretin response data (27 cases)

NAME	TOTAL VOL.	MAX. BICARB.	TOTAL AMYL-ASE	PANC. FUNCT.	ICT. IND. CURVE	OPERATIVE FINDINGS OR HOSPITAL COURSE
Cholecystectomy						
G. D.	2.2	104	21.2	N	C	Dilated CD due to stenosis of Papilla of Vater
S. C.	1.2	25	3.8	Insuff.	B	Inflammatory mass at head of pancreas
S. S.	6.0	133	6.5	N	C	Cicatricial stenosis of Common Duct with hepatodochoduodenal fistula
C. G.	3.4	134	22.4	N	D	Cicatricial stenosis of Common Duct with duodenocutaneous fistula
E. M.	4.7	89	11.4	N	B	CD Normal—Biopsy—Biliary Cirrhosis
E. M.	3.2	99	21.8	N	B	Jaundice subsided on ward
T. Z.	2.1	79	1.8	Insuff.	B	CD Normal—Biopsy—Subacute Pancreatitis
S. G.	2.7	89	14.6	N	B	Jaundice subsided on ward
O. F.	3.4	90	14.6	N	B	Biliary cirrhosis
T. S.	2.5	106	6.0	N	B	CD Normal in size, ball valve CD stone
A. A.	2.3	108	8.3	N	C	Cicatricial stenosis of Common Duct with hepatodochoduodenal fistula
S. S.	3.4	112	9.5	N	C	CD stones with dilated Common Duct
Non-cholecystectomy						
R. F.	2.0	78	4.0	Insuff.	B	Metastatic Carcinoma
G. W.	4.8	101	30.7	N	B	Chr. cholecystitis and choledocholithiasis
N. G.	2.7	59	2.2	Insuff.	A	Chronic Pancreatitis
M. Z.	3.1	88	18.9	N	B	Stenosis of distal Common Duct
B. G.	3.8	99	15.6	N	B	Chr. cholecystitis and choledocholithiasis
J. M.	3.7	104	3.7	Insuff.	D	Carcinoma of Papilla of Vater
P. M.	2.7	133	19.7	N	D	Chr. cholecystitis and choledocholithiasis
J. N.	1.4	99	1.8	Insuff.	D	Carcinoma of Common Duct and Head of Pancreas
B. D.	1.1	38	4.5	Insuff.	D	Metastatic Carcinoma
L. O.	1.9	113	34.0	N	D	Pancreas Normal—Ca of Common Hepatic Duct
J. N.	5.5	93	24.2	N	B	Chr. cholecystitis and choledocholithiasis
J. H.	2.6	106	15.9	N	B	Choledocholithiasis and choledochoduodenal fistula
A. C.	0.5	44	0.4	Insuff.	D	Carcinoma Head of Pancreas
J. L.	1.0	24	0.2	Insuff.	D	Carcinoma Head of Pancreas
B. G.	1.2	100	5.3	Insuff.	D	Carcinoma Head of Pancreas

secretion, all of whom were explored and were discovered to have pancreatic lesions. Seven of these 10 had carcinoma of the pancreas, and three had pancreatitis. Fifteen of the remaining 17 cases with normal pancreatic response,

exhibited no pancreatic lesions at operation. Two were not explored because of subsidence of jaundice.

For analysis of the biliary pigment responses, these 27 cases were grouped into two categories: cholecystectomy and non-cholecystectomy. In the non-cholecystectomized group, 8 patients had abnormal pancreatic secretion (discussed above) and 7 had normal pancreatic response with abnormal biliary pigment curves. Five of the latter had calculus disease of the gall bladder, the common duct, or both. A sixth patient had a carcinoma of the common hepatic duct, and the remaining one a stenosis of the papilla of Vater. Thus all seven had biliary tract disease. Among the 12 cholecystectomized patients, there were five instances of incomplete common duct obstruction and dilatation predicted on the basis of a type C response. The confirmatory operative findings were common duct obstruction due to stricture in four cases, and to stones in one case. Five patients had normal pancreatic secretion and normal icterus index curves despite jaundice. Two of these patients had biliary cirrhosis; two others had transient jaundice treated conservatively; and the last had a ball valve choledochal stone without dilation of the common duct. The remaining two of these twelve cases were discussed above as having pancreatitis with abnormal secretin findings. Thus, the secretin test in non-hepatic jaundice affords a more accurate localization of the pathology. When the pancreatic response is abnormal, the lesion lies in the head of the pancreas. When the pancreatic function is normal, but the biliary pigment response is abnormal, the site of the disturbance is between the pancreas and the liver—in the biliary tract proper. Normal pancreatic and biliary function in this group is highly suggestive of liver disease.

#### SUMMARY

Precise delineation of the secretin response in normal patients and in those with pancreatic disease must await statistical analysis of data from a large series, studied with a uniform, accurately standardized secretin preparation. The observations in the present report are of a preliminary nature only; in spite of the large number of patients studied, the individual groups, as yet, are small.

In acute pancreatic inflammatory disease, the secretin test is of limited value. During the first week of illness, when abnormalities are most likely to be encountered, the test is often difficult to perform. During the second week of illness, although clinical symptoms persist, recovery of functioning parenchyma may occur so that negative findings do not exclude the diagnosis. All cases of proved chronic relapsing pancreatitis showed marked abnormality of pancreatic secretion. If this finding is confirmed by further study, accurate and reliable diagnosis of chronic pancreatitis will be possible.

Neoplasms of the pancreas cause changes in pancreatic secretion by virtue of obstruction to the pancreatic ducts. Such obstruction in the body or head of the pancreas significantly reduces the quantity of functioning parenchyma; lesions of the tail most likely do not. In contradistinction to chronic pancreatitis, where the most characteristic change in the secretin response appears to be depression of bicarbonate values, the alteration in pancreatic secretion in malignancy is a lowering of the volume response with less change in the concentration factors.

The combined determination of pancreatic function and biliary pigment response is of considerable significance in patients with persistent symptoms following cholecystectomy, and, in jaundice. In the post-cholecystectomy syndrome group, a small number of pancreatic lesions can be uncovered. Valuable information can also be obtained concerning the patency of the biliary tract. One type of response shows promise of being pathognomonic of incomplete common duct obstruction. In hepatitis, the secretin test does not give distinctive results; in obstructive jaundice, on the other hand, secretin studies enable more precise localization of the disease within the pancreas and biliary tract.

The results of this study of pancreatic function with secretin (145 cases) confirm the impression of previous investigators that the test has diagnostic potentialities.

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# THE EFFECT OF ENTEROGASTRONE CONCENTRATES ON GASTRIC SECRETION IN HUMAN BEINGS

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## INTRODUCTION

This investigation was undertaken because of the interest which has been shown in the effect of enterogastrone upon the course of peptic ulcer in human beings<sup>1-3</sup> and because further information on its action in man seemed indicated. We have studied the effect of enterogastrone concentrates on the gastric secretory response of human beings to the injection of histamine and to the ingestion of a test meal.

When we undertook this investigation, information on the action of enterogastrone in man was very scanty. Ivy<sup>1</sup> had indicated that with the 200 mg. doses of enterogastrone used in therapeutic trials very little direct or immediate depression of gastric secretion would be expected in human beings. Later he and his co-workers reported<sup>3</sup> that the protection afforded peptic ulcer patients by enterogastrone could not be explained on the basis of the action of enterogastrone in inhibiting gastric secretion. During the progress of our study Pollard, Block and Bachrach<sup>4</sup> presented a summary of their observations on 5 patients with intractable duodenal ulcer. They observed no consistent reduction in the fasting output of hydrochloric acid from the stomachs of these patients when treated for at least three months with enterogastrone by mouth. With 200 mg. of enterogastrone given parenterally they noted a transitory inhibition of motility and secretion. While this manuscript was in preparation the excellent reports of Kirsner, Levin and Palmer<sup>5, 6</sup> appeared. They found<sup>5</sup> that nocturnal and twenty-four hour fasting gastric secretion in patients with peptic ulcer may be decreased by the intramuscular injection, in divided doses, of large quantities of an enterogastrone concentrate (1,000 to 3,000 mg.). The effect was variable and somewhat unpredictable. The major action was a reduction in the concentration of hydrochloric acid in the juice. In a second study<sup>6</sup> the enterogastrone concentrate reduced the acid output of the stomach in only two of eleven tests in which histamine was used as a stimulant. The total quantities of the enterogastrone concentrate injected ranged from 400 to

2,000 mg. With 1,000 mg. doses of the concentrate, the secretion induced by injection of insulin was unaffected although larger doses may have modified the response. The results of our tests made with histamine are in agreement with those of the above-mentioned authors. The effect of enterogastrone on the secretory response to a meal in human beings has not, as far as we know, been reported before.

#### METHODS AND PROCEDURE

*Enterogastrone preparations.*—The enterogastrone concentrate used for parenteral administration was supplied through the courtesy of Drs. Frank Visscher and H. F. Hailman of The Upjohn Company. It was prepared according to methods developed by Greengard, Ivy and their collaborators from hog's intestinal mucosa<sup>3, 7</sup>.

The enterogastrone extract used for oral administration was supplied through the courtesy of Wilson & Company Inc. and Eli Lilly & Company. It was prepared by a much simpler procedure than that employed for the material administered parenterally. It consisted essentially of a lyophilized acid extract of mucosa from the upper 2 to 6 feet (60 to 180 cm.) of hog's intestine.

*Control tests for potency of enterogastrone preparation used in this study.*—The antigastric secretory activity of the enterogastrone concentrate used for parenteral administration was tested by Dr. Frank Visscher in the research laboratories of The Upjohn Company on anesthetized rats with the pylorus ligated. The method of assay was the same as that employed by Dr. Visscher in other studies of enterogastrone<sup>8</sup>. The assay was carried out before we started our study, then later when we had completed our investigation it was repeated on samples of the enterogastrone we had used and stored in Rochester.

As a further check on the activity in the material used for parenteral administration we tested its effect on histamine-provoked gastric secretion from Heidenhain pouches in 4 dogs. We are grateful to Dr. J. H. Grindlay for the preparation of the Heidenhain pouches in these dogs. The body weight of the dogs ranged from 9.5 to 11.5 kg. Before each test the animals fasted for eighteen hours. Histamine in doses of 0.025 to 0.075 mg. (base) was given subcutaneously every ten minutes throughout the test. The juice secreted during successive fifteen-minute periods was collected separately. When secretion had attained a consistent rate, usually within the first hour of the test, juice was collected for two to five consecutive fifteen-minute periods for determination of the control rate of secretion. Then the enterogastrone concentrate dissolved in 5 cc. of normal saline was injected intravenously in doses ranging from 50 to 400 mg. The rectal temperature was checked before and after the injection. Signs of toxic reaction such as weakness, salivation, retching, vomiting and changes in heart rate were watched for carefully throughout each test.

The average acid output in milligrams of hydrochloric acid for the fifteen-minute control periods was compared to the average fifteen-minute output of acid during the first and second hours after the injection of the enterogastrone preparation.

*Tests on human volunteers.*—Two types of tests were made. In the first, enterogastrone concentrate was given parenterally between the first and second injections of histamine in a double histamine test. In the second, a milder stimulus, in the form of a test meal, was used, larger doses of the enterogastrone concentrate were injected and, in addition, the oral preparation was administered.

In preparation for the tests the subjects fasted approximately fourteen hours. During the tests they lay on their left sides and were instructed not to swallow saliva. The contents of the stomach were first aspirated through a soft Sawyer tube. Then samples of the gastric contents were collected separately during successive fifteen-minute periods. A definite effort was made to empty the stomach at the end of each fifteen-minute period. The volume of each fifteen-minute sample was measured and the free and total acidity determined by titration with tenth-normal sodium hydroxide, Töpfer's reagent and phenolphthalein being used as indicators.

*Double histamine tests.*—In these investigations, 10 adult male volunteers were studied. Four were normal and 6 had active duodenal ulcers. The technic employed was essentially that used by Klumpp and Bowie<sup>9</sup> and by Rivers and Vanzant<sup>10</sup>. After the stomach had been emptied, continuous suction was applied to the Sawyer tube in an effort to obtain as complete collection of the juice secreted as possible. When two or three fifteen-minute samples of fasting juice had been obtained, the first subcutaneous injection of histamine diphosphate in a dose of 0.01 mg. per kilogram was given. Seventy-five minutes later a second similar injection of histamine was given. In 7 of the subjects thirty minutes before the second injection of histamine, 200 mg. of the enterogastrone concentrate dissolved in 5 cc. of 0.5 per cent solution of chlorobutanol in water, was injected deep into the gluteal muscles. In the 3 other subjects the injection of the concentrate was given at the same time as the second injection of histamine.

*Test meal studies.*—In these studies, 14 volunteers were used. Six were healthy males, 7 had duodenal ulcers and 1 had gastric ulcer. The test meal consisted of eight arrowroot cookies and two glasses of water. The meal was consumed in about five minutes. One hour later the Sawyer tube was passed and the stomach emptied. The tube was left in place and specimens were collected every fifteen minutes for five consecutive periods. Several days later the same procedure was repeated except that, in addition, enterogastrone was administered as follows: On the day before the test the subject took 3 capsules

(approximately 4.5 gm.) of the enterogastrone preparation for oral administration after each meal and at bedtime. When he reported in the morning at the laboratory 200 mg. of the enterogastrone concentrate was injected intramuscularly. The test meal was given an hour later. Then an hour after the meal had been given and just before passage of the tube, a second injection of 200 mg. of the concentrate was given.

### RESULTS

*Control tests of potency.* In rats.—The enterogastrone preparation used in this study for parenteral administration to human beings when tested by Dr. Visscher produced a reduction to  $\frac{1}{3}$  or  $\frac{1}{4}$  of the control value in the volume of gastric juice secreted by rats after pyloric ligation. Tests made before and

TABLE 1

*Effect of the enterogastrone concentrate used in this study upon gastric secretion in rats with pyloric ligation\**

CONTROL TESTS		ENTEROGASTRONE TESTS (20 MG. PER KILOGRAM GIVEN INTRAVENOUSLY)	
Animals	Average volume of gastric secretion, cc.	Animals	Average volume of gastric secretion, cc.
Results before study of action on human beings			
5	1.8	2	0.6
4	2.1	3	0.5
Results after study of action on human beings			
6	1.9	5	0.6

\* These tests were carried out by Dr. Frank Visscher, Research Laboratories, The Upjohn Company.

after our studies on the human being gave practically identical result (table 1). According to the results of these tests, the preparation contained an inhibitor of gastric secretion.

In dogs.—Two or more determinations were made on each of the 4 dogs with Heidenhain pouches (table 2). Doses of 200 to 400 mg. of the enterogastrone concentrate were given on four occasions. They consistently lowered the acid output of the pouches. The reduction ranged from 25 to 99 per cent. In this dosage range a reaction, however, always occurred. The rise in rectal temperature ranged from  $0.2^{\circ}$  to  $1.5^{\circ}$  F. As a rule the animals urinated, defecated, retched and showed some weakness. One animal collapsed. Recovery was rapid. In all instances the animals appeared normal within one hour. In every instance the inhibition of gastric secretion persisted long after the toxic reaction had subsided. Of the six tests in which 100 mg. of the concen-

trate was given, decisive inhibition occurred in five. Mild reactions occurred on four occasions. These consisted of salivation and retching with little or no restlessness or weakness. The symptoms usually lasted only five to ten minutes. In 1 animal (animal C, table 2), however, recovery was not complete until thirty minutes had elapsed. As in the case of the 200 mg. doses the inhibition persisted, indeed often reached its maximum, after the symptoms of the reaction had disappeared. Two doses of 50 mg. were given to 1 dog;

TABLE 2

*The effect of enterogastrone concentrate on output of hydrochloric acid from Heidenhain pouches in dogs receiving histamine*

DOG	MG. OF HISTAMINE EVERY 10 MINUTES	INTRAVE- NOUS DOSE OF ENTERO- GASTRONE	MEAN OUTPUT OF HYDRO- CHLORIC ACID PER 15 MINUTES BEFORE AND AFTER ENTERO- GASTRONE			PER CENT CHANGE FROM CONTROL		RECTAL TEM- PERATURE CHANGE	DURATION OF TOXIC REACTION		
			After		First hour	Second hour					
			Before	First hour		First hour					
		mg.	mg.	mg.				°F.	min.		
A	0.05	50	42.0	41.2	28.9	-2	-31	+0.2	0		
	0.05	100	51.5	53.4	53.9	+4	+6	+0.8	0		
	0.05	200	44.1	21.9	6.4	-51	-86	+0.2	30		
	0.025	50	30.7	31.5	31.6	+3	+3	+0.7	0		
	0.025	100	18.7	16.5	7.5	-12	-60	+0.7	10		
B	0.075	100	23.6	20.5	15.9	-13	-33	+1.5	0		
	0.075	200	18.0	11.9	13.6	-34	-25	+1.0	45		
	0.075	400	20.5	11.6	8.5	-48	-59	+1.5	60*		
C	0.5	100	26.7	2.7	2.2	-90	-92	+0.1	30*		
	0.5	100	24.9	5.6	11.9	-76	-52	+1.0	5		
D	0.5	100	36.0	26.4	32.8	-27	-9	-1.1	5		
	0.5	200	33.2	4.4	0.4	-90	-99	-0.8	60*		

\* This dog showed marked inhibition of gastric secretion well into the third hour, long after the toxic reaction had subsided.

neither caused toxic symptoms, but one produced a 31 per cent inhibition of secretion, while the other had no effect on secretion.

It has been concluded from these studies that the concentrate used for parenteral administration in human beings contained an inhibitor of gastric secretion. The occurrence of inhibition in the absence of toxic manifestations in two tests and the uniform persistence of inhibition after subsidence of the reaction indicated that the inhibiting effect of the extract was, in part at least, independent of its toxic action. Still, the separation was not always decisive and we were left with the conclusion that either the enterogastrone itself was

toxic in the dogs we studied or a separate toxic factor or factors were present in the extract. The experience supported our hesitancy in giving large doses of this material to human beings.

*Studies on human volunteers.*—Since no differences were noticed between normal subjects and subjects with peptic ulcer, the results of the tests in these two groups have been combined.

Double histamine tests.—In five of the seven tests in which 200 mg. of the enterogastrone concentrate was injected a half hour before the second injection of histamine, the free and total acidity reached slightly higher values after the second than after the first or control injection of histamine. The volume of secretion, as obtained by continuous suction, was less after the second

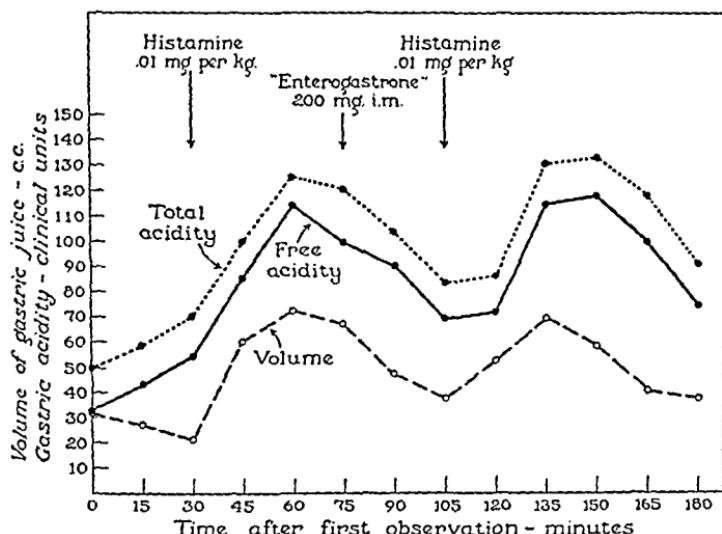


FIG. 1. Mean acidity and volume of gastric secretion in 7 subjects during double histamine tests. Enterogastrone concentrate was administered between the injections of histamine.

injection of histamine than after the first in four tests and greater in three. The variability in the volume of juice obtained was large.

Although the results as obtained in the above-mentioned procedure indicated that the concentrate had had little or no effect upon the secretion of gastric juice, the data were subjected to two further analyses. In the first, the means of the values obtained in the study of the 7 subjects for each fifteen-minute period were calculated and plotted graphically (fig. 1). There was a slight average increase in the free and total acidity and some decline in the volume of the juice secreted after the second injection of histamine. The differences, however, did not appear to be significant. In the second analysis, the mean of all of the values for the five fifteen-minute periods during which

TABLE 3

*Effect of entero gastrone concentrate on double histamine test in 7 subjects\*†*

RESPONSE TO CONTROL INJECTION OF HISTAMINE, MEAN VALUE			RESPONSE TO INJECTION OF HISTAMINE AFTER "ENTEROGASTRONE," MEAN VALUE		
Volume cc.	Acidity, degrees		Volume cc.	Acidity, degrees	
	Free	Total		Free	Total
56.2 ± 6.1	91.7 ± 4.6	106.3 ± 4.6	50.6 ± 5.6	95.8 ± 5.5	111.6 ± 5.4

\* Mean values for 35 fifteen-minute samples of gastric juice collected during one and a quarter hours after each injection of histamine.

† Values after the ± signs are the standard errors of the means.

TABLE 4

*Comparison of response to test meals given with and without entero gastrone concentrate in 14 human beings*

MINUTES AFTER TEST MEAL	WITHOUT ENTEROGASTRONE		WITH ENTEROGASTRONE		DIFFERENCES	
	Mean*	Standard deviation	Mean*	Standard deviation	Mean†	Standard deviation‡
Free acidity, degrees						
60	58.3 ± 4.5	16.8	60.4 ± 4.5	16.8	-2.1 ± 3.0	11.1
75	59.9 ± 6.1	22.8	66.6 ± 5.7	21.4	-6.7 ± 6.6	24.8
90	52.8 ± 6.4	23.8	60.2 ± 4.3	16.0	-7.4 ± 6.7	25.0
105	53.2 ± 7.7	28.9	54.3 ± 5.9	22.0	-1.1 ± 4.9	18.4
120	52.0 ± 6.3	23.4	48.9 ± 5.8	21.6	+3.1 ± 5.8	21.5
135	49.0 ± 6.3	23.7	50.8 ± 7.0	26.1	-1.8 ± 9.1	34.1
Volume, cc.						
60	145.7 ± 13.1	49.0	160.8 ± 26.8	100.1	-15.1 ± 20.9	78.2
75	21.1 ± 1.9	7.1	28.6 ± 3.1	11.5	-7.5 ± 3.8	14.2
90	32.3 ± 3.5	13.0	28.7 ± 2.6	9.7	+3.6 ± 3.9	14.5
105	20.4 ± 3.0	11.1	21.3 ± 2.7	10.1	-0.9 ± 2.6	9.9
120	19.6 ± 2.5	9.4	21.5 ± 3.6	13.4	-1.9 ± 3.1	11.4
135	25.9 ± 4.8	18.0	24.2 ± 3.8	14.4	+1.8 ± 3.9	14.7
Total acidity, degrees						
60	79.5 ± 4.3	16.1	79.9 ± 4.1	15.3	-0.4 ± 3.1	11.8
75	76.8 ± 5.4	20.1	83.2 ± 5.1	19.0	-6.4 ± 6.3	23.6
90	72.7 ± 6.6	24.6	77.3 ± 4.3	16.0	-4.6 ± 6.9	25.7
105	68.5 ± 7.6	28.4	72.0 ± 5.9	21.9	-3.5 ± 4.9	18.3
120	66.6 ± 6.8	25.3	65.5 ± 5.8	21.6	+1.1 ± 6.4	23.6
135	63.7 ± 6.3	23.4	67.1 ± 6.1	22.9	-3.4 ± 7.5	28.1

\* The values after the ± signs are the standard errors of the means.

† The values after the ± signs are the standard errors of the mean difference for paired data.

‡ Standard deviation of individual differences.

juice was collected following the first injections of histamine was calculated and compared with the mean of all of the values for the five fifteen-minute periods following the second injections. The values are given in table 3. They indicate that the injection of the enterogastrone concentrate was without effect upon the response to the injection of histamine. The mean values for acidity were indeed slightly higher after the second than after the first injection of histamine. Since these results are practically identical to those obtained by others<sup>9-11</sup> after two successive and equal injections of histamine administered under *control* conditions, the conclusion has been drawn that the injection of the enterogastrone concentrate in our study had no effect upon the gastric secretory response to histamine. Similar results were obtained on the 3 subjects in whom the concentrate was injected at the same time as was the second dose of histamine.

Test meal studies.—To summarize and to allow ready comparison of the results obtained on the 16 volunteers, the mean values for the acidity and volume of all the samples obtained during each fifteen-minute period have been determined for the control tests and for the tests with enterogastrone preparations (table 4). Examinations of these data show that there was no significant difference between the tests with and those without enterogastrone.

Reaction to injection of the enterogastrone concentrate.—One subject complained of transitory weakness shortly after an injection of 200 mg. No other symptoms indicative of a generalized reaction occurred and there was no rise in oral temperature in any of the subjects. Practically all of the subjects complained of pain and some swelling at the site of the injection.

#### COMMENT

The extract of hog's intestinal mucosa used in this study for parenteral administration certainly inhibited gastric secretion in rats and dogs but the immediate conclusion that this was due to *enterogastrone* was tempered somewhat by the fact that toxic reactions, sometimes severe and lasting up to one hour, accompanied its use in dogs. Two of the chief features of the reaction were salivation and retching. Atkinson and Ivy<sup>12</sup> and Grossman, Woolley, Dutton and Ivy<sup>13</sup> have clearly shown that nausea itself will inhibit gastric secretion in dogs although recovery will usually occur in from 30 to 160 minutes after the nausea. In our studies, inhibition always persisted for 120 minutes after the injection and, when tests were made, was also present during the third hour after the injection. It seems unlikely that the inhibiting effect of the nausea, present often for only five to ten minutes at the start of the test, would have persisted for so long.

Besides the nausea, the pyrogenic effect of the extract may also have contributed to its inhibiting action on gastric secretion in the dogs<sup>11</sup>. However,

upon three occasions when 31, 86 and 92 per cent inhibition occurred, the rise in temperature at no time exceeded 0.2° F. Also, the rise in temperature in the experiments of Meyer, Cohen and Carlson<sup>14</sup> which produced pronounced inhibition in gastric secretion were usually much greater than the maximal rise of 1.5° F. recorded in our tests. The conclusion seems warranted that enterogastrone was present in the extracts we used. Still, it was not in as purified a state as that generally employed by Ivy and his co-workers in establishing its action on gastric secretion. Contaminating substances most probably accounted for the hyperpyrexia and reactions we encountered, and since these may have contributed to the effects we observed we have regarded the material we used as a mixture which may have contained more than one biologically active substance.

Because contaminating substances may have prevented enterogastrone action in human beings, we do not feel that our results can, at this time, be interpreted to indicate that pure enterogastrone will be without action in similar tests on human beings. Much larger doses of purified material will have to be given before such a conclusion can be drawn.

Determination of the volume of gastric secretion by the continuous suction method used in this study is not accurate. Changes in volume of the juice secreted may have occurred without detection. It is conceivable that if reduced secretion occurred with reduced motor activity, the amount of juice lost through the pylorus would be less and any reduction in secretion might be offset by accumulation in the stomach. The volume recovered might then be unchanged despite an actual change in the amount secreted. While this possibility cannot be eliminated, it seems likely that had any pronounced reduction occurred in the volume of juice secreted in our tests it would have been detected. The lack of any effect upon acidity of the juice supports the conclusion that 200 mg. doses of the enterogastrone concentrate used in this study were without effect on human gastric secretion.

Our results with histamine are in complete accord with the finding by Levin, Kirsner and Palmer<sup>6</sup> that the intramuscular injection of 400 to 2,000 mg. of enterogastrone concentrate does not significantly affect the secretory response of the human stomach to single or repeated injections of histamine.

The close similarity between the secretory response to the two test meals was somewhat surprising (table 3). The results were less variable than those obtained by Klumpp and Bowie<sup>9</sup>. This may have been due to a difference in technic. They aspirated the contents of the stomach and replaced all but 10 cc. every fifteen minutes after the meal was fed. We waited one hour after giving the meal before withdrawing any samples. Then the stomach was emptied and samples were collected every fifteen minutes without anything being returned at any time to the stomach. The repeated withdrawal and

replacement of the gastric contents in the tests by Klumpp and Bowie may have stimulated irregularities in motility and secretion not present in our study. Also, it seems likely that the major part of the juice we collected arose from the intestinal phase of the secretory response to the meal while that obtained by Klumpp and Bowie was, in the main, due to the gastric phase of secretion.

#### SUMMARY

1. The effect of enterogastrone preparations (extracts of the upper part of the small intestine of hogs) on gastric secretion has been studied in 20 human volunteers and 4 dogs with Heidenhain pouches.
2. Enterogastrone concentrate given intravenously in amounts of 100 mg. or more inhibited the output of acid in nine of ten tests in the dogs with the Heidenhain pouches. Inhibition occurred in one of two tests in which 50 mg. was used. Toxic reactions, varying from mild to very severe, occurred after the administration of the concentrate intravenously to the dogs. The effects noted included some rise in temperature, salivation, retching, weakness and, in 1 case, collapse.
3. Enterogastrone concentrate given intramuscularly to 10 human volunteers in doses of 200 mg. did not affect significantly the gastric secretory response to histamine during a double histamine test. The results are in complete accord with the finding of Levin, Kirsner and Palmer<sup>6</sup> that an enterogastrone concentrate in doses of 400 to 2,000 mg. was without significant effect upon gastric secretory response of patients to single and repeated injections of histamine.
4. Enterogastrone extracts given to 14 human volunteers in doses as large as 400 mg. intramuscularly and 18 gm. orally did not significantly affect the gastric secretory response to a modified Ewald test meal.

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## CASE REPORTS

### HYPERPLASIA OF BRUNNER'S GLANDS SIMULATING DUODENAL POLYPOSIS

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We are reporting a case of hyperplasia of Brunner's glands simulating duodenal polyposis, representing the first, in our experience, in which adequate preoperative clinical and roentgen studies were done. The details of the case are of interest from the point of view of differential diagnosis and events following surgery. A review of the literature reveals a paucity of information concerning similar types of cases.

#### CASE REPORT

R. S. L., Hospital No. 182529: A 36 year old white male was hospitalized on Nov. 3, 1947 because of roentgen evidence of multiple polyp-like projections in the proximal duodenum. The polyps first were recognized 7 months prior to hospital admission. The only immediate subjective complaint was a tendency to loose stools which had been present for about a year, numbering approximately 4 to 6 daily. The stools varied from formed to watery consistency with an absence of recognizable mucus or blood. Seven months prior to admission a severe secondary anemia was recognized elsewhere and apparently improved with the use of iron and liver preparations. The past medical history otherwise was negative. There was an 8 pound weight loss in the past year. Physically the patient was asthenic, slight, somewhat pale and showed no obvious abnormality.

Shortly before the present admission to the hospital roentgen examination of the duodenum by a barium meal revealed a number of small rounded opacities, which appeared more prominent than those reported 7 months previously. The polyp-like defects shown on roentgen study were confined to the duodenal cap and proximal portion of the descending loop of the duodenum. No tenderness was elicited over the site of the defects. Some of the prominence probably was more apparent than real due to the fact that duodenal compression technic was used in the later examination. One of the polyps-like defects in the superior portion of the duodenal cap seemed much larger than the surrounding defects, in comparing the two sets of films, and suggested the possibility that it was, in fact, a growing tumor. In retrospect, the altered appearance of the duodenal cap probably was related to uneven compression of that region during the examination, since the subsequent operative specimen revealed a surprising uniformity in the size and shape of the duodenal projections.

There was an absence of roentgen defects elsewhere in the small and large bowel. Fractional gastric analysis with an Ewald test meal showed a fasting acid of 127

units of free hydrochloric acid and 144 units of total acid. The peak acid figures, occurring at 105 minutes, were 150 units of free hydrochloric acid and 168 units of total acid.

Gastroscopy on Nov. 1, 1947 revealed a normally appearing gastric mucosa without evidence of polyposis. The most distal portion of the antrum was not visualized.

Routine blood count, sedimentation rate, prothrombin time, serum proteins with A-G ratio, serum bilirubin, serum amylase, and lipase and serologic test for syphilis were all normal. Five stools were examined for occult blood by Gregerson method, of which 2 were negative and 3 were +3.

The patient was discharged on Nov. 11, 1947 and readmitted for operation on Dec. 8, 1947. One week prior to Dec. 8, 1947 he developed severe epigastric pain for the first time and vomited once. The pain was sharp, gripping, doubled him up and was associated with loose stools.



FIG. 1. Roentgenogram of duodenum on 10/22/47 showing multiple small rounded filling defects due to hyperplasia of Brunner's glands.

On Dec. 13, 1947 a laparotomy was performed by W. H. E. using a transverse incision. The duodenum felt thick although single individual polyps could not be felt. The pyloric sphincter was opened. The mucosa of the duodenum was heaped up in folds. A specimen of one of the folds was removed for frozen section which failed because of technical difficulties. The mucosa seemed more normal near the ampulla of Vater. Approximately 3 inches of the distal stomach and 3 inches of the proximal duodenum were removed in one piece. In dissecting the duodenum free from the pancreas the outlet of the duct of Santorini was preserved. The line of resection was one centimeter proximal to the ampulla of Vater. The common duct was not injured. A V-shaped excision of the anterior wall of the stomach made the circumference of the stomach equal to that of the duodenum. A routine two layer anastomosis was done, using cotton for the outer layer and cat gut for the inner layer. The abdomen was closed in layers.

The following pathologic report of the excised specimen was recorded: "The total length of the specimen is 15 centimeters after fixation. The circumference of the

stomach is 7.5 centimeters. The mucosa of the duodenum is abnormal in appearance, giving the impression of cobble-stones". There appeared to be about 12 rounded prominences on the surface of the duodenum, each varying from 4 to 8 millimeters in diameter and 2 to 3 millimeters in height. In each instance the base was broad. Microscopically the soft projections were reported to be due to hyperplasia of the glands of Brunner. There was no evidence of tumor formation.

Following the operation the patient developed an anemia with following comparison of pre- and post-operative blood counts:

	12/10/47	12/19/47
RBC.....	5,070,000	2,620,000
HB.....	15 gms.	7 gms.



FIG. 2. Resected specimen. Folds and pseudopolyps in duodenum on the left.

The cause of the anemia was not obvious since no great amount of blood was lost at operation and there was no post operative melena. Unfortunately no stools for occult blood were recorded in the immediate post-operative period. On 12/25/47 the stool occult blood was negative.

The post-operative fractional gastric analysis was done on 12/27/47. The fasting gastric contents titrated 107 units of free hydrochloric acid and 122 units of total acid. The peak of 118 units of free hydrochloric acid and 136 units of total acid at 60 minutes seemed to represent a reduction from the preoperative figures.

During the period following 12/21/47 the patient complained greatly of severe epigastric pain radiating to the back together with nausea and intermittent vomiting. The use of hourly feedings of milk and cream with antacid hourly on the half hour failed to control his symptoms. A continuous intranasal gastric drip was only partially successful in controlling his pain, and attempts to discontinue the drip were followed by increased severity of the pain.

On Dec. 29, 1947 an x-ray examination of the operative site by barium meal showed a partial resection of the distal portion of the pylorus and the first portion of the

duodenum with a Billroth No. I type of anastomosis. There was slight coarsening of the mucosal pattern of the stomach, slight narrowing at the site of the ostomy with irregularity of the mucosal pattern just proximal to the ostomy as well as irregularity of the contour of the stomach. These changes are considered to be postoperative in nature.

The patient was discharged from the hospital on Dec. 31, 1947. Because of continued symptoms the patient was readmitted to the hospital and a barium meal on

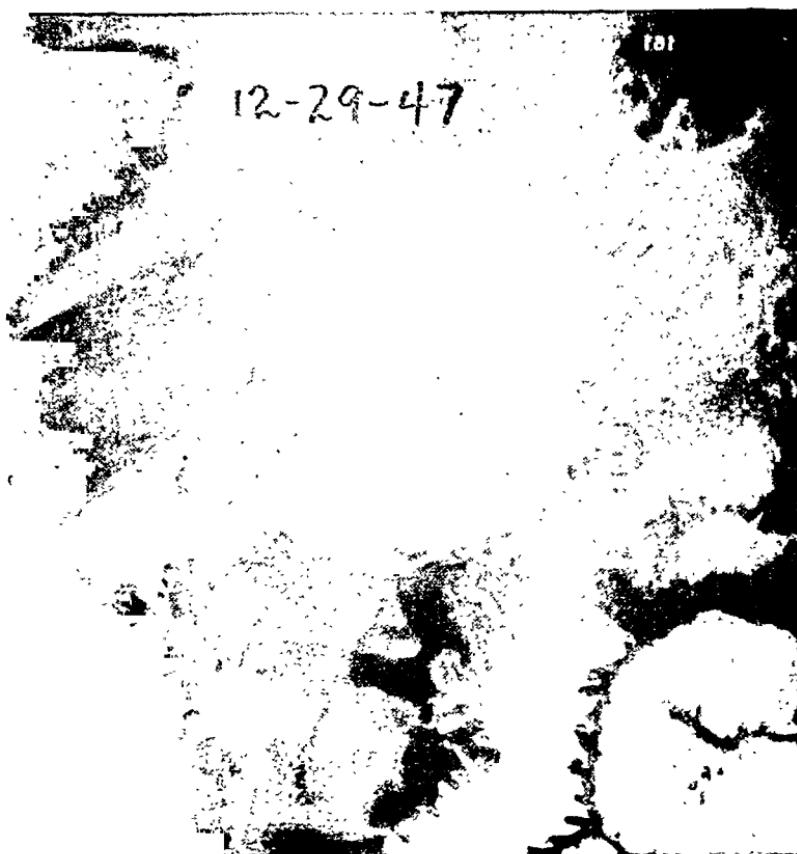


FIG. 3. Eight days postoperative (12/29/47) roentgenogram showing site of gastro-duodenostomy with irregularity of the mucosal pattern just proximal to the ostomy.

Jan. 12, 1948 showed a large ulceration proximal to anastomosis. After failure of conservative measures a supradiaphragmatic vagotomy was done on Jan. 17, 1948. Every effort was made to make this a complete vagotomy. The oesophagus was mobilized for a distance of 10 cm. The two main vagi trunks and 5 to 6 additional strands were divided. No strands could be palpated in the wall of the oesophagus as it was lifted from its bed.

An insulin tolerance test was done on Feb. 2, 1948 showing a fasting gastric acid

of 120 units of free hydrochloric acid and 142 units of total acid. The maximum insulin effect in the blood sugar occurred at 45 minutes, (blood sugar 38 mgms. per cent) at which time the free acid was 57 units and total acid 78 units. The test was interpreted as indicating continued vagal influence on the gastric secretion in spite of the vagotomy.

The patient's severe pain and intermittent vomiting persisted. On March 4, 1948 re-examination of the operative site by barium meal confirmed the presence of a large defect interpreted as a marginal ulcer.



FIG. 4. Definite large triangular fleck seen on 1/12/48 representing a large ulceration.

On March 11, 1948 a subtotal gastrectomy was performed by W. H. E. There was induration around the duodenum. Dissection revealed a large ulcer crater at the posterior suture line, involving the pancreas. The ulcer seemed more on the gastric than on the duodenal side of the suture line. The ampulla of Vater was in the wall of the ulcer. Bile squirted from the opening of the ampulla of Vater. Conventional closure of the duodenum would have obstructed the common duct, therefore, the anterior wall of the duodenum was sutured to the base of the old ulcer crater in the pancreas. A very high subtotal gastric resection was done.

Postoperatively the patient did well and was symptom free on March 31, 1948, the date of discharge. Roentgen examination of the operative site by a barium meal on March 31, 1948 showed a well functioning gastro-jejunostomy. On March 17, 1948 a specimen of fasting gastric juice showed no free hydrochloric acid and 50 units of total acid.

On April 20, 1948 gastric analysis under controlled fluoroscopic guidance revealed a fasting acid of 31 units free hydrochloric acid and 42 units total acid. A maximum acid value of 54 units free hydrochloric acid and 73 units total acid was reached at 105 minutes.

#### DISCUSSION

The original diagnosis in this case was polyposis of the duodenum. Because of the possible precancerous nature of this condition, a radical resection of the duodenum was contemplated. The frozen section taken at the time of the first operative procedure was inadequate to correct our misconception. Therefore, at the time, the original resection was considered the most conservative procedure feasible. Later events proved that this was an error in judgment.

The high gastric acidity should have been a warning that the defects seen on x-ray were not due to polyps. Cassidy and Macchia state that achlorhydria is present in almost all cases of duodenal polyposis reported when gastric analysis was done.

The prompt development of a marginal ulcer following resection of the first portion of the duodenum leads one to speculate on the relationship of hyperplasia of Brunner's glands to the high gastric acidity this patient had. Was this a protective mechanism? Florey and Harding expressed the belief that the normal secretion of Brunner's glands by virtue of its mucin and alkaline content protects the duodenal mucosa from damage by the acid gastric juice and inferred that malfunction of these glands might be primarily responsible for duodenal ulcer. The train of events in this case adds further credence to that hypothesis.

#### SUMMARY

A case of hyperplasia of Brunner's glands simulating duodenal polyposis is reported in which resection was rapidly followed by a marginal ulcer. The possibility of some relationship between Brunner's glands and peptic ulcer is mentioned.

## ULCERATED GASTRIC LIPOMA

LAUREANO FALLA ALVAREZ, M.D., JOSÉ S. LASTRA, M.D. AND PEDRO LEÓN, M.D.

*From the University Hospital, School of Medicine, University of Havana*

Gastric lipoma is one of the rarest benign tumors of the stomach and a review of the available literature shows that compared to other such tumors of this organ, very few cases have been reported. This tumor may be present during the lifetime without symptoms ever arising, being in some cases only found at necropsy.

Up to 1940 only 32 cases had been reported in the literature, when Rumold<sup>1</sup> collected them all. Five years later, Scott and Brunschwig<sup>2</sup> reproduced Rumold's tabulation of cases adding six more observations (including their own case), the total number of reported cases amounting to 39.

To both revisions of former cases we are able to add the report by Burmeister<sup>3</sup> in 1932, who describes an ulcerated lipoma located at the greater curvature of the stomach and in 1946, the reports of Moricheau-Beauchant and associates<sup>4</sup> who recorded another intra-gastric lipoma and the case described by Hobbs and Cohen<sup>5</sup> of invagination into the duodenum, due to a submucosal lipoma; finally, we are reporting the case that, we presume, brings the number of published cases up to 44.

Of these gastric lipomas we found that the ones reported by Spitzmuller<sup>6</sup>, White and Judd<sup>7</sup>, Mandl and Vogl<sup>8</sup>, Melchior<sup>9</sup>, Glass<sup>10</sup>, Garré and Garelk<sup>11</sup>, Rumold<sup>1</sup> and Burmeister<sup>3</sup>, were complicated, like our case, by ulceration or erosion; as a rule this complication as well as other inflammatory changes, bleeding, hemorrhage or pyloric obstruction, give rise to the symptoms that induces the patient to visit the physician.

The origin of gastric lipomas remains unknown; some authors suggest a congenital influence, others are inclined to believe in metaplastic, heteropic, inflammatory or neurocirculatory factors, but no essential etiological agent has been found. Their localization is variable, but the most frequent site is the distal half of the stomach or pyloric region where they may produce obstructive symptoms. Development may be either subserosal, projecting outward from the stomach cavity, or submucosal, projecting into the cavity. Gastric lipomas may be single or multiple, sessile or pedunculated; they have the characteristics of adipose tissue and it is not uncommon to observe ulceration or erosion. The evolution, if complications do not interfere, is very slow and silent and in most cases eventually discovered by x-ray studies or autopsy. The most frequent complications are of mechanical origin: pyloric obstruction or prolapse through the pylorus or from an inflammatory origin: erosion, ulceration, bleeding and hemorrhage.

The clinical picture is similar to that of other benign tumors of the stomach. The diagnosis can often be made by x-ray examination and by gastroscopy, surgical removal being the only possible treatment.

#### CASE REPORT

In 1945, the patient D. R., a 45 year old, white married woman, came to our office complaining of mid and left epigastric pain, radiated to the precordial region, which she had been suffering for the previous two years. The pain, variable in intensity, had a sudden onset increasing in severity during the last months and making its predominant appearance late after meals and at midnight. Relief was obtained by food

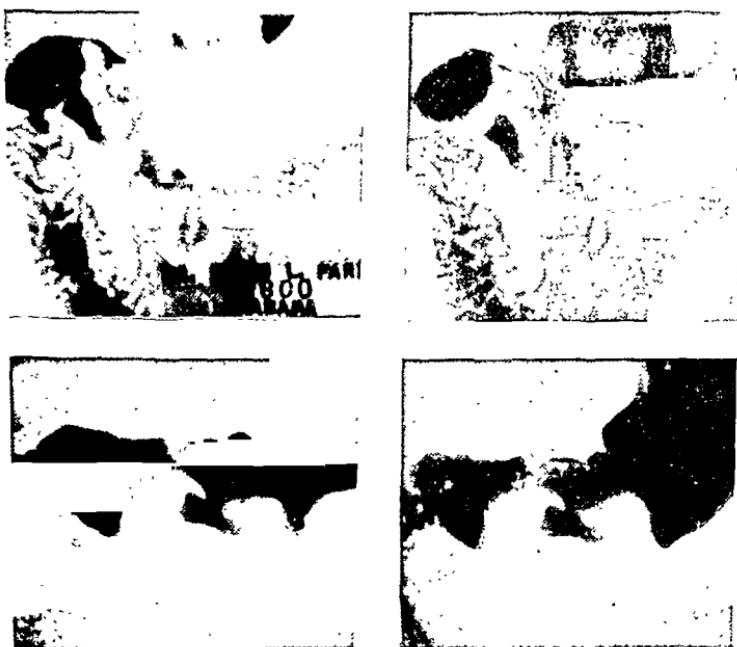


FIG. 1. Large and irregular shoeshaped niche penetrating in a round tumoral mass of the greater curvature of the antrum.

These attacks were accompanied by a liquid stool the following morning (unrepeated the rest of the day) and by evening fever for the previous weeks. The patient, an obese person of 61" height and 181 pounds, had not lost weight throughout her illness nor had her appetite diminished. Her family, marital and past history, was negative.

Physical examination was essentially negative with the exception of a first grade gingivitis and tachycardia with accentuation of the second aortic sound; the abdomen was distended, diffusely painful and very difficult to palpate because of her excessive adipose subcutaneous tissue. Laboratory studies reported nothing of significance; gastric analysis showed: Grade I hyperacidity. Electrocardiogram was normal.

Gastroscopy could not be performed because of lack of cooperation on the part of the patient.

Roentgenologic examination of the stomach (Dr. P. L. Fariñas, Fig. 1) reported as follows: "Large and irregular shoeshaped niche penetrating in a round tumoral mass at the greater curvature of the antrum, producing a pressure defect at the base of the duodenal bulb".

Primary peptic ulcer is excluded because of shape and localization; malignancy was almost ruled out because of the sharply outlined tumoral mass and the excellent aspect

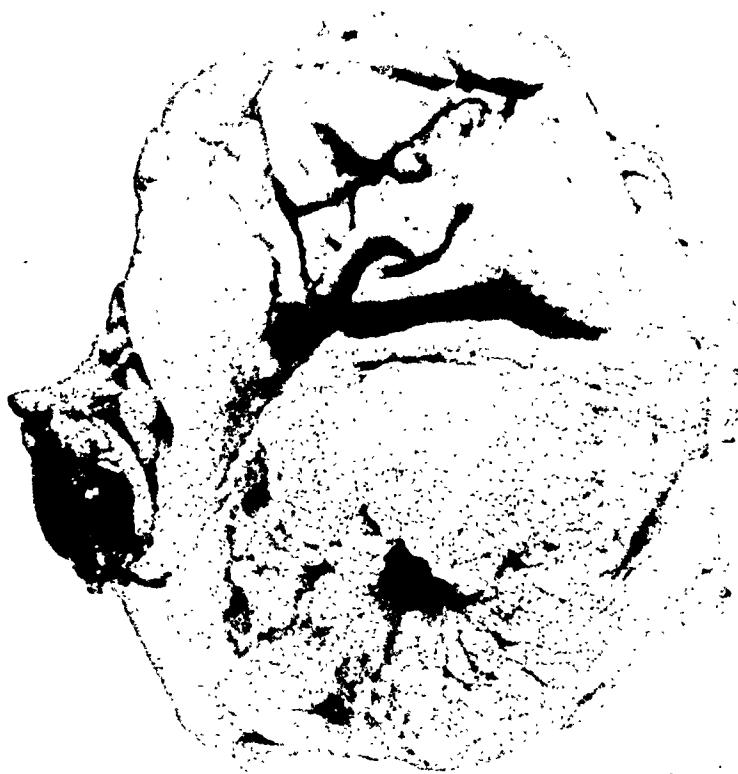


FIG. 2. Surgical specimen showing the prominent tumor mass and hypertrophic mucosa with ulcer crater.

and nutritional condition of the patient after two years with symptoms, so we were inclined to the clinical diagnosis of an ulcerated benign tumor of the stomach.

Operation was carried on by one of us (J. S. L.) on August 14, 1945. Under continuous spinal anesthesia, the abdomen was opened through a transverse incision; on exploring the stomach a tumoral mass was found at the antrum, the size of a small orange. It was firm to palpation and the serosa overlying it, was not altered. No glands were involved and the rest of the abdominal exploration was negative.

Sub-total gastrectomy was done with transmesocolic gastrojejunial anastomosis (Reichel-Hofmeister-Finsterer). Five grams of Sulfanilamide were powdered in the peritoneal cavity and the abdomen was closed in layers.

The operation was difficult, technically, on account of the obesity of the patient and lasted almost three hours, but she stood it very well and was dismissed on the eleventh postoperative day after an uneventful recovery.



FIG. 3. Section through the tumoral mass with the characteristics of a lipoma 5 x 4 cm. The ulcer penetrates the tumor 1.5 cm.



FIG. 4. Panoramic photomicrograph of a complete section of the tumor mass.

The report of the pathologic examination (P. L.) was as follows:

"The specimen consists of the distal two-thirds of the stomach with a prominent tumoral mass located in the antrum. Inspection of the mucosal surface reveals hypertrophic mucosa with an ulcer crater in its more prominent portion (Fig. 2).

In a section through this, there appears a tumor mass with the characteristics of a lipoma, circumscribed, ovoid, 5 x 4 cm. in size, yellowish, translucent and of elastic consistency. The tissue of the surrounding submucosa, forms a fibrous condensation of varying thickness. The ulcer is deep and penetrates the tumor to an extent of about 1.5 cm. (Figs. 3 and 4).

The microscopic examination of the tumoral mass shows it to consist of mature adipose tissue, with abundant fibrous stroma (Fig. 5). Surrounding the ulcer is observable a zone of infiltration of inflammatory tissue.

From the relative abundance of fibrous stroma, the histopathological diagnosis appears to be that of a fibro-lipoma.

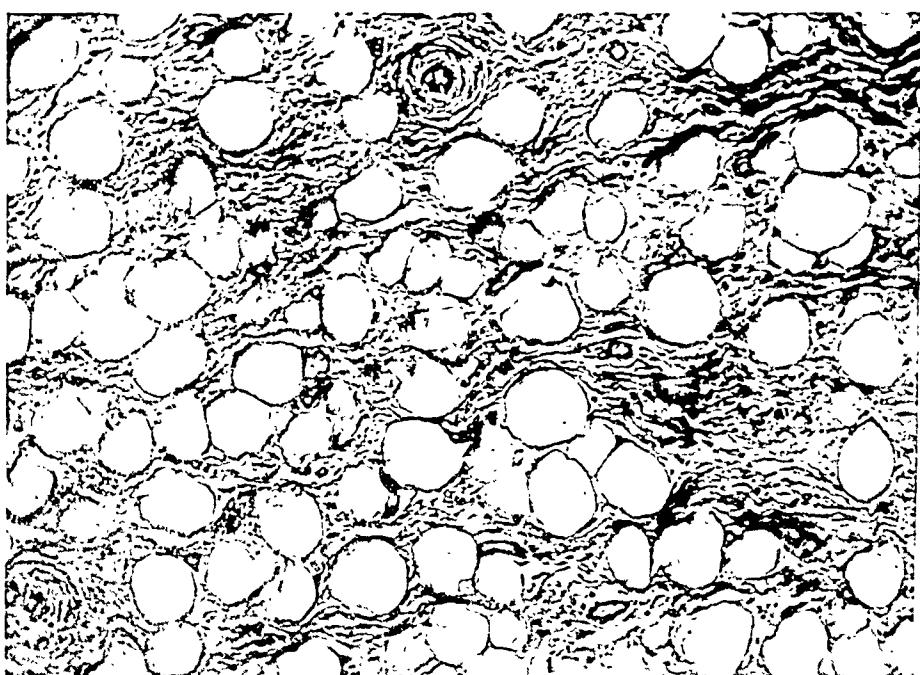


FIG. 5. Photomicrograph of the tumor mass showing the mature adipose tissue with fibrous stroma.

#### SUMMARY

A case of ulcerated submucosal gastric lipoma is reported.

A brief review of the literature has been made and added 4 more cases of gastric lipomas to Rumold's and Scott-Brunschwig's previous tabulations of cases, bringing the total number of published cases up to 44, which proves that this benign tumor of the stomach is rarely encountered.

In our case a crateriform ulcer penetrated in the tumor mass, a complication observed in 8 more of the reported cases.

The diagnosis of gastric lipoma is seldom made before operation. In our case we were lead to suspect a benign tumor of the stomach, because the x-ray picture showed a sharply outlined tumor mass and the patient's two year his-

tory of mild symptoms together with her excellent physical condition, which suggested it was not malignant.

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## CASE OF PORTAL CIRRHOSIS OF THE LIVER WITH UNUSUAL ABDOMINAL MASSES DUE TO EDEMATOUS APPENDICES EPIPLOICAE

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The patient, a white male aged 48, entered Indianapolis General Hospital on September 5, 1947 complaining of swelling of the abdomen and respiratory embarrassment. He had noticed progressive enlargement of his abdomen for 6 months, and swelling of the ankles, shortness of breath and abdominal pain for 2 months. During that time he had gained 60 lbs. in weight. He had jaundice in April, 1944, the cause of which was not determined.

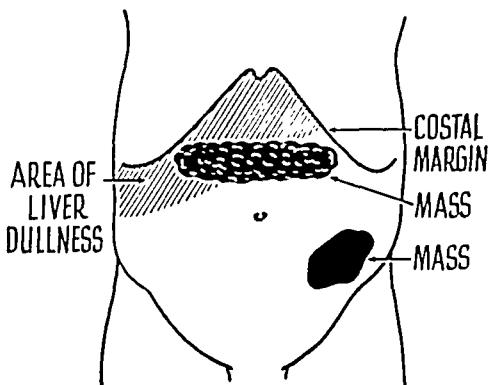


FIG. 1

He was a chronic alcoholic and his dietary habits were poor. The patient appeared well nourished and well developed. His skin and sclera were tinted yellow. The abdomen was tense and hugely distended with fluid. The veins over the abdomen were enlarged. Spider naevae were present on the face, shoulders, arms and chest. The patient had moderate palmar erythema. There was marked pitting edema of the legs and ankles. The papillae of the tongue were moderately atrophic and there was angular stomatitis. Blood pressure was 170/110. The pulse was 120/min. On examination of the chest there were inspiratory and expiratory moist rales. The diaphragm was elevated bilaterally.

After removal of some ascitic fluid by paracentesis, a mass was found to extend about 6 inches below the right costal margin which was felt to be the liver, and the spleen was thought to be palpable. There were two other masses palpated in the abdomen. One was located in the epigastrium between the liver and the anterior abdominal wall extending from the right upper quadrant to the left upper quadrant.

\* Fellow in Gastroenterology.

TABLE I

	1947						1948											
	Sept. 9	Sept. 18	Sept. 23	Oct. 2	Oct. 9	Oct. 17	Oct. 24	Oct. 31	Nov. 3	Nov. 14	Dec. 23	Jan. 12	Jan. 16	Jan. 23	Jan. 30	Feb. 6	Feb. 12	Feb. 18
Alkaline phosphatase	21.0	18.6	13.5	15.6	13.2	—	12.3	12.0	15.0	—	18.4	11.4	17.3	11.1	11.7	9.3	10.6	
Total protein	7.3	6.7	7.5	7.7	7.3	8.4	8.8	8.0	8.4	—	7.5	6.8	7.5	7.7	6.9	7.2	7.5	
Albumen	2.7	2.8	3.1	2.6	2.6	2.9	3.1	2.5	2.9	—	2.6	2.7	2.1	1.8	2.4	2.6	2.8	
Globulin	4.6	3.9	4.4	5.1	4.7	5.5	5.7	5.5	5.5	—	4.9	4.1	5.4	5.9	4.5	4.6	4.7	
Serum bilirubin	9.20	4.50	2.56	1.77	1.61	1.24	1.13	1.36	0.68	—	0.68	0.97	0.97	0.6	0.5	0.6	0.68	
B.S.P. % re-tention:																		
in 30 minutes	31%																	
in 45 minutes	20.9%																	
Ceph. chol. floe:																		
24 hour	4+	2+	2+	2+	2+	2+	2+	2+	2+	2+	2+	3+	3+	1+	1+	1+	1+	2+
48 hour	4+	3+	3+	3+	3+	1	1	2	1	2	1	2	3	2	2	2	2	3+
Thymol turbidity (as units)	1	4	2	2	2	1	1	2	1	2	1	2	3	2	2	2	2	3+
Weight	235-224.225	232	219	222	222	219	217	223	211	*	276-240.227	234.204	206	204	212	212	216	
Paracetamol*	**									*								

Strengers . . . . (January 12, 1948)

Futouugh . . . . (November 15, 1947)

Reddinfield . . . . (December 10, 1947)

The mass was large, cylindrical, slightly nodular, firm, freely movable, and it displaced the abdominal wall anteriorly. The other mass was located in the left lower quadrant in the region of the sigmoid colon. It was similar to the first, being large, cylindrical, slightly nodular, firm and freely movable. Its upper and lower limitations could not be circumscribed. Manipulation caused some pain. (See Figure 1.)

The urine contained bile and was otherwise negative. The hemoglobin was 13.5 Gm., erythrocytes 4.5 millions, leucocytes 12,700 with 71% adult neutrophiles, 23% lymphocytes, 3% monocytes, 2% eosinophiles and 1% basophiles. The Kline and



FIG. 2

Kahn tests were negative. The specific gravity of the ascitic fluid was 1.012 and it contained less than 4% total protein. Other data are listed in Table I.

X-ray studies with barium were made of the esophagus, stomach and duodenum and of the colon. No abnormalities were noted. The gall bladder did not visualize at x-ray with double dose dye technique.

For the first three weeks, frequent abdominal paracenteses were necessary. Mercurial diuretics were then used and the frequency of paracenteses was reduced.

Exploratory surgery was recommended because the nature of the abdominal masses was uncertain. The patient requested that he be allowed to go home and

return for surgery at an early date. This was arranged. The patient did not return, however, until abdominal distention with respiratory embarrassment made it imperative. He had been drinking alcohol in large quantities for 15 days prior to readmission. The patient was prepared for surgery, and an exploratory laparotomy was done by Dr. John E. Owen. 11,000 cc. of ascitic fluid were removed. The liver was small and extremely fibrotic. The spleen was enlarged approximately three times normal size. The omentum and mesentery of the large bowel and the ap-

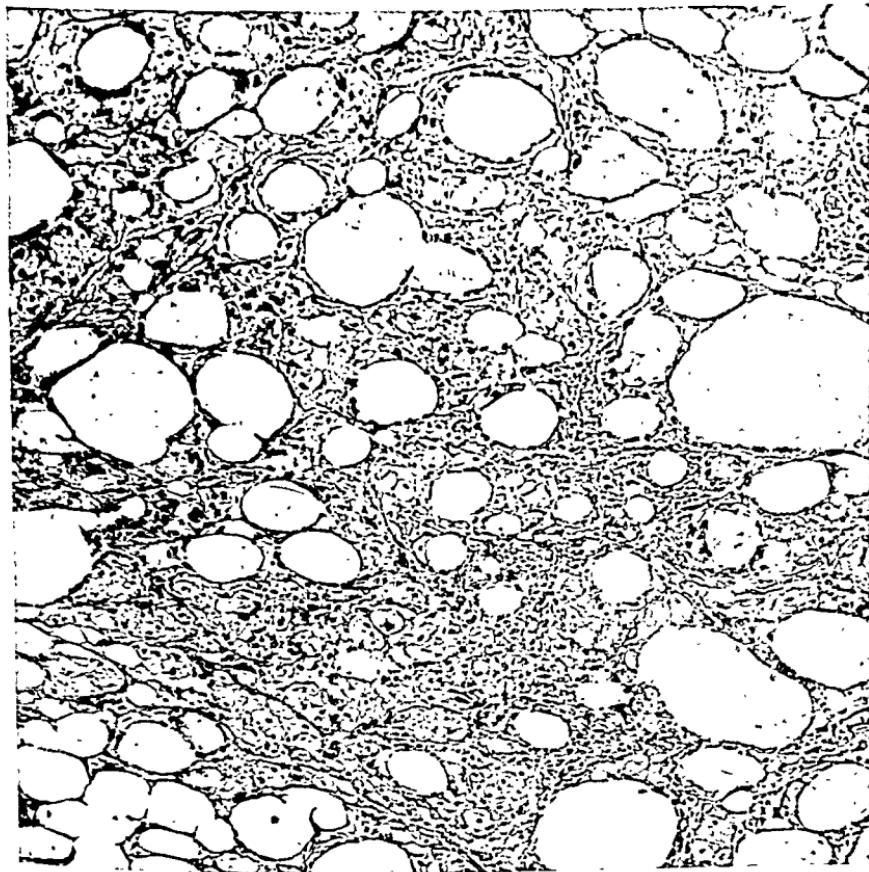


FIG. 3

pendices epiploicae were extremely edematous and large. No other masses or abnormalities were found. A biopsy was taken from the liver and an appendix epiploica was removed for pathological study. An omentopexy was done.

The section of liver was grossly nodular and the cut surface showed fibrous nodularity. The section showed fibrosis around the liver lobules with moderate lymphocytic infiltration and very minimal fatty infiltration. No biliary retention was apparent. The diagnosis was portal cirrhosis (Fig. 2).

The appendix epiploica was 1.8 cm. in length. It was rather opaque. The section showed fat necrosis and moderate fibrosis with moderate cellular infiltration, predominately lymphocytic. There were some nondescript groups of cells, among which appeared a few multinucleated cells. The diagnosis was adipose tissue with chronic degeneration, edema and fibrosis (Fig. 3).

#### SUMMARY

This is a report of a patient with cirrhosis of the liver, portal hypertension and ascites who was subjected to exploratory surgery because two unusual masses were palpated in the abdomen, in the region of the transverse and sigmoid colon. Routine diagnostic procedures failed to show the nature of the masses. At surgery it was determined that the appendices epiploicae were so extremely large and edematous, apparently from portal obstruction, that the transverse and sigmoid colon had been palpated as large, cylindrical, firm, nodular, movable masses. The omentum and mesentery of the large bowel were also large and edematous, but they and the remainder of the colon had not been palpated at physical examination having been obscured by ascitic fluid.

## EDITORIALS

### WHAT STARVATION DID TO THE NERVOUS SYSTEM OF THOUSANDS OF PRISONERS OF WAR

It is unfortunate that in the past thirty years so much of dietetics has been worked out on the rat and then assumed to be valid for man. This assumption was made in spite of the fact that what was true for the rat was not always true for the guinea pig or for the chick or the calf. For years observant physicians, capable of independent thought, have puzzled over the fact that the women they see with anorexia nervosa, or with the habit of living for years on only a few mouthfuls of food a day, usually show no sign of any known deficiency disease. Such a woman may go down to 80 pounds and yet be active and wide-awake and without any sign of injury to the nervous system or eyes or skin. Evidently something has been wrong with our theories.

Also, years ago when the British sent a commission to Japan to study thousands of poor persons living on a diet decidedly subnormal in vitamin B, they were puzzled to find so little beriberi. They found instead shortness of breath on exertion. Curiously, the incidence of beriberi, when plotted on a map, showed that the trouble afflicted mainly persons who lived on the edges of streams! Some Japanese researchers said also that beriberi did not come until the victim was infected with a certain bacterium. These observations were not according to theory and hence were largely ignored and soon forgotten. Unfortunately, we human beings love to make things simpler than they are, especially in textbooks.

It is curious that during all these years since vitamins were discovered, research workers in dietetics have not taken the trouble to go into the slums of the Orient, where millions live out their lives close to starvation, to see what really happens to such persons. Almost everyone who has described sub-clinical avitaminoses has described them as they are supposed to occur in the United States, the richest country in the world, where a high percentage of the people have all they need to eat.

At last, we who are interested in diet are being supplied with ample data in regard to human starvation, data obtained in the horrible detention camp in the Orient and Germany. There, brutal and conscienceless men inadvertently carried out one of the greatest dietetic experiments the world has ever seen. They left hundreds of thousands of human beings on an inadequate diet until they either died or were reduced to skin and bones. In a recently published book Spillane\* reviewed much of what is known about the results of this

\* Spillane, John D. "Nutritional Disorders of the Nervous System." Baltimore, The Williams & Wilkins Company, 1947, 280 pages.

experiment. He has the great advantage of having worked with a number of medical officers who were themselves captives and who for years lived with the prisoners whose symptoms they observed and recorded.

As might have been expected, if only from the old experience of sailors with scurvy, it was soon noted that some individuals got into trouble while others got by fairly well; also members of certain races tended to cave in and get a deficiency disease sooner than did members of other races.

As Spillane said at the start of his book, contrary to general opinion, starvation does not ordinarily produce scurvy, pellagra or beriberi, even when the period of deprivation is sufficiently prolonged to allow for such developments. Curiously, a deficiency disease is more likely to develop if a fair amount of poorly chosen food is ingested. A diet deficient in vitamin B<sub>1</sub> is more likely to cause trouble if it contains much carbohydrate. It appears from this that there is a factor of intoxication bound up in the carbohydrate.

Dietary deficiency in man is always a complex disturbance. Unfavorable conditions such as those met with in concentration camps do not leave the victims suffering from deprivation of only one vitamin. Only the ingenuity of man can produce such a diet. Usually there are multiple deficiencies not only in vitamins, but in amino acids, protein, chemical elements, and calories.

In the detention camps it was found that a diet lacking in the B complex might produce pellagra in an occasional individual and beriberi in another. Furthermore, beriberi might show itself with edema, cardiac failure, or acute injury to nerves. Some persons showed destructions of certain nerves or nerve tracts, while others suffered injury to parts of the brain. Startling was the fact that a man, while retaining the outward appearance of fair health, might lose his sight or his hearing as the result of nutritional failure.

As Spillane said after seeing hundreds of these prisoners of war go down to skin and bones without developing the expected avitaminoses, he lost what little faith he had in his ability to diagnose the so-called subclinical deficiencies. He felt that those who do this sort of thing must really be guessing. He doubted, also, if the symptoms of the supposed subclinical avitaminoses would necessarily be the ones which were observed at the onset of the major deficiency syndromes as they were seen in the camps of Germany, Malaya or Hong Kong. As Spillane said, in England, in spite of a rather restricted diet, the neurologist rarely finds any syndrome that he can say definitely is due to a vitamin deficiency, "and this, despite the efforts of pharmaceutical firms to persuade him to the contrary!" Furthermore, "in spite of a low ration of vitamin B in the British Isles, pellagra is extremely rare."

It may have been that some of the troubles of the badly starved prisoners of war were due to the lack of certain amino acids in the diet. According to

Spillane, a study of this field of human dietetics may prove to be as fertile a one as that of the avitaminoses.

The experience of the war prisoners suggests that the retina is one of the most delicately adjusted mechanisms of the nervous system, and one which can suffer much from starvation and lack of oxygenation. Spillane stated that achlorhydria is a common finding in pellagrins but an uncommon one in cases of beriberi. It may clear up on treatment with nicotinic acid.

It has been demonstrated of late that in man some vitamins can be synthesized in the bowel. In his chapter 12, Spillane discussed briefly the diarrheas which were seen in the concentration camps and which may have been due in part to malnutrition. Necropsy in such cases showed widespread degeneration of the mucous membrane of the gut. Commonly, there were degenerations, also, of the peripheral nerves, posterior root ganglia, posterior nerve roots, and the posterior columns of the spinal cord.

A very interesting clinical finding was the interrelationship of pellagra, sprue and subacute combined degeneration of the cord. In all of these conditions there were anorexia, flatulence and diarrhea. Glossitis, achlorhydria and atrophic changes in the mucosa of the gut were common. In these cases the giving of nicotinic acid did not help much.

Hyperchromic anemia has been observed in only some 4 per cent of pellagrins. Interestingly, a pellagrous type of skin eruption sometimes appeared in cases of tropical sprue. Harris, in 1941, described the very illuminating case of a man who, in 1916, had classical pellagra; in 1921-1926 typical pernicious anemia; and later, bouts of typical sprue whenever he failed to take his liver extract. There have been other similar reports suggesting a close relationship between these diseases. Degeneration of the peripheral nerves and of the posterior and lateral columns of the spinal cord has been noted often in pellagrins, but seldom in cases of tropical sprue. Common to pellagra, sprue and primary anemia was the finding, at necropsy, of fatty degeneration of the liver.

It was interesting that in many of the cases, when the armistice came and medical officers started to treat the walking skeletons in the camps, they found that thiamine alone did not help much. About all it did sometimes was to relieve pain. To really get well, first the prisoners had to get on a good general diet. The medical officers could not ascribe the retrobulbar neuritis, nerve deafness, ataxic and spastic paraplegias to deficiencies of thiamine, nicotinic acid or riboflavin alone. As already noted, it seemed obvious that multiple deficiencies had been at work. It is probable, also, that some of the more serious injuries to the nervous system were due to added insults such as those connected with the coming of dysentery or malaria or parasitic infections of the bowel.

It is curious that among the cranial nerves the optic and auditory ones suffered the most. There was no obvious reason why in one case the posterior columns of the spinal cord suffered badly while in others it was the pyramidal tracts which were destroyed.

Evidently, in spite of all of this tremendous amount of cruel, murderous experimenting on human beings, we still have much to learn about the mode of action of dietary deficiencies in man. Certainly every serious student of dietetics will want to read Spillane's valuable book.

W. C. A.

## COMMENT

### FAILURE OF VAGOTOMY TO HELP DOGS WITH MANN-WILLIAMSON FISTULAS

Recently, Saltzstein, Sandweiss, Hill and Hammer reported the effects of vagotomy on 12 dogs with Mann-Williamson fistulas. It didn't do any good; the dogs died rapidly, several from gastric dilatation. Four died within a month before they had time in which to develop an ulcer; the other two died thirty-eight to sixty-one days postoperatively.

W. C. A.

### THE INABILITY OF HISTIDINE TO PROTECT DOGS WITH MANN-WILLIAMSON FISTULAS FROM DEVELOPING ULCER

In a recent paper, Saltzstein, Sandweiss, Hill and Hammer reported that in 14 dogs with a Mann-Williamson fistula, the giving of histidine had no effect. Actually, from a scientific point of view, there never has been any good evidence on which to base the treatment of ulcer with histidine. The craze started after a clinical paper was published in Europe. The drug in a proprietary form was welcomed because it gave physicians something to do for the patient each day. Another proprietary remedy called "aolan," said to be a solution of lactalbumen, and sold to be injected into patients with ulcer, was tried by Saltzstein and associates and was found also to have no effect in the protection of dogs with Mann-Williamson fistulas.

W. C. A.

### THE ANTI-PERNICIOUS ANEMIA FACTOR IN LIVER OR VITAMIN B<sub>12</sub> HAS BEEN CRYSTALLIZED

After twenty-two years of research on the purification of liver extracts and identifying the substance which so promptly helps patients suffering from pernicious anemia, E. L. Rickes, N. G. Brink, F. R. Koniuszy, T. R. Wood and Karl Folkers from the laboratories of Merck and Company, have recently announced the isolation and crystallization of a substance which has a pronounced effect in doses of from 2 to 5 micrograms. In another paper, M. S. Shorb reported the accelerating activity of this substance on the growth of *Lactobacillus lactis*, and Randolph West, of Columbia University, reported on the great effectiveness of it in cases of addisonian anemia. The three papers are to be found in the April 16, 1948, number of *Science*.

Work is now in progress on the chemical identification of the new vitamin and all biochemists and physicians will await with eagerness further publications from the Merck group. . They are to be congratulated on a splendid piece of work.

W. C. A.

## VAGOTOMY IN THE TREATMENT OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS

In view of the fact that after vagotomy some persons and many animals suffer from a debilitating and sometimes incurable or fatal diarrhea, it is curious now to see the operation being used for the treatment of diseases of the bowel which are associated with severe diarrhea. It is curious also to find surgeons attempting to cure a colonic disease by cutting two nerves which, according to most anatomists and physiologists, may not reach the colon or have much influence on it. There is only a little evidence to indicate that in some animals a few fibers of the vagi reach the proximal third of the colon. The literature on the subject has been summarized by Alvarez in *An Introduction to Gastroenterology*.

It is all the more curious to attempt to treat diarrheas with an operation which was found, in rabbits, to greatly increase the irritability of the small bowel. Cutting these nerves appeared to take a sort of brake off of the bowel so that it responded violently to every stimulus. It would appear, then, that the only logical reason for cutting the vagi in cases of diarrhea would be the hope that thereby the diarrhea-producing effects of anxiety and fear and panic would be blocked. If this were true, the operation should be performed only in those cases in which organic disease in the terminal ileum and colon is complicated by a bad psychologic situation. To be sure the loosening effects on the bowel of worry and unhappiness and fear are well known to every clinician and many a layman, and it may well be that some persons with true colitis would recover if they could be freed from the bad effects of anxiety over their situation.

Actually, in the March 1948 number of *Minnesota Medicine*, Dennis, Eddy and Westover reported the results of transthoracic vagotomy undertaken in twenty-two cases of idiopathic ulcerative colitis, and in one case of functional diarrhea. One patient died of cardiac complications before the vagotomy could be completed; two are definitely worse, and the condition of three more is unchanged. Fourteen have improved, and three, at the time of writing, had not been under observation long enough for evaluation of the procedure. Two of the excellent results occurred in patients suffering also with regional enteritis. In general, the best results were obtained in cases in which the duration of symptoms had been short and the amount of scarring in the bowel minimal.

Laboratory studies by Wangensteen, Friesen and Lillehei, not yet published, on vagotomy in dogs failed to reveal any resulting abnormality in the digestive enzymes or in the motor activity of the ileum.

In the patients operated on by Dennis, Eddy and Westover there was the usual marked slowing of gastric emptying, the stomach rarely being empty of barium in twenty-four hours, and usually containing some of the material after forty-eight or even seventy-two hours. This sort of thing in man usually produces constipation. As every good clinician knows, one of the first symptoms of obstructing carcinoma near the pylorus is often constipation. There was a prolongation of transit of the material through the small intestine, even when the stomach began to empty fairly early. It would appear that in man vagotomy does not make the bowel as irritable as it does in rabbits.

Two of the patients who have been freed of symptoms had a negative result from the insulin test, suggesting that section of the vagi was incomplete. Eight patients who, before operation, had blood, pus and mucus in the stools were much improved after vagotomy, with better formed excrement.

Interestingly, Dennis et al. report that in the experience of Dr. Russell Wilson tetraethylammonium bromide, which appears to relax markedly the gastro-intestinal muscle and to stop peristalsis, had an adverse effect in five cases of ulcerative colitis.

One of the best cases to show that in man incomplete vagotomy can at least temporarily slow the progress of material through the small bowel was that of the first patient operated on by Dennis and his associates, a twenty year old girl who had previously had all of her colon and five sixths of her ileum removed for severe ulcerative colitis and ascending enteritis. She had undergone ileostomy. After a vagotomy, which could not be completed because of her poor condition, she passed the first solid excrement she had had in four years. There was a gain in weight and a temporary return of fair health. Later, more vagus fibers were resected but no improvement followed this operation.

As Dennis wisely says, it will be a year or two before he and his colleagues can tell what the end-results of this daring operation are to be.

W. C. A.

## BOOK REVIEWS

UP FROM THE APE. *Earnest Albert Hooton*. The Macmillan Company. New York, Revised Edition, 1947, 788 pages.

This is a splendid book and one that is crammed with interesting material, interesting to any philosophically minded physician. Medicine is really a branch of anthropology and, as every wise physician knows, certain groups are more inclined to suffer from certain diseases than are other groups. There is also developing of late a science of the anthropology of the individual as related to disease. Some physicians think now that certain physical builds make a person more subject to tuberculosis, or ulcer, or gallstones, or schizophrenia, or hypertension. Some of the troubles of man are also relicts of diseases that still bother our remote cousins, the apes.

Of late some remarkable skulls have been found, particularly in South Africa, Java and China, which show what man was like when he was not much different from an ape. Hooton has gathered together this information and presented it in a most interesting way.

In the book there are some splendid pictures of the several anthropoid apes.

This is a splendid book for a physician to read for sheer delight as well as for much information of value to him.

LIFE. ITS NATURE AND ORIGIN. *Jerome Alexander*. Reinhold Publishing Corporation. New York, 1948, pp. 291, price \$5.00.

This book, written by an eminent consulting chemist, is packed with information derived from several fields of biology and chemistry, and is one of the most interesting books the reviewer has ever read. Every educated physician would find delight and profit in perusing this volume.

Alexander has tried to figure out how life may have originated on this earth and how it has developed along evolutionary lines. He has devoted his life to biological and chemical research; he is internationally known as a student of colloid chemistry, and has written a number of standard texts on this subject. He is particularly interested in the catalizers and these, he believes, are the most efficient tools of nature in the process of evolution. He believes that the genes, those units of tissue which determine hereditary transmission, are made up of catalysts. He is much interested in the recent discovery that molecules can serve as a sort of mold or template for the reproduction of enormous numbers of similar molecules. This book could have been written only by a man who had an enormous knowledge not only of chemistry but of genetics and biology. Very interesting is his comment on page 197 that certain fermentations can be trained to handle certain sugars which originally they could not ferment.

Like a good scientist, Alexander gathers together all the facts which he could get from many fields and gives them to his readers for what they are worth. One is happy to see that Alexander does not try to prove scientifically that there is a God in the heavens who is running the earth in a kindly way and taking loving care of all

of us. He is not a "reconciler." This is an immensely more valuable but less uplifting book than the best-seller written by Le Compte de Nouy.

THUS WE ARE MEN. *Sir Walter Langdon-Brown, M.D.* Longmans, Green and Company. New York, 1939, pp 344.

Although this book is now out of print and hard to come by, it is so delightful and so full of information about many authors and eminent physicians, and so full of inspiration that the reviewer feels compelled to call it to the attention of the readers of Gastroenterology. All those many physicians who have delighted in the writings of Sir William Osler will delight also in this book. Sir Walter Langdon-Brown was Professor of Physics at the University of Cambridge, England, also Consulting Physician to St. Bartholomew's Hospital. Many years ago he had a decided interest in psychosomatic medicine and often he wrote beautifully and clearly on this subject.

The chapters in this book are largely reprints of memorial or special lectures which Sir Walter gave during his later years. It is immediately evident that he was not only a master of the practice of medicine but also one of the best educated of the world's physicians. He had the same type of education in the humanities which Osler had. He knew some of the great writers of England and he knew their intimate stories. For instance, he writes delightfully and intimately of Sir William Osler, Robert Bridges, James Barrie and Robert Louis Stevenson. There are splendid chapters on The Biology of Social Life, The Return of Aesculapius, "Just Nerves," New Pains for Old, The Psychology of Authorship, Dr. Jekyll Diagnoses Mr. Hyde, The Background to Harvey, Some Gods and their Makers, The Plague in England, and The Evolution of Death.

The book is filled with sentences that the reader will want to mark and memorize and go back to again and again. For instance, "to see things as they are is the task of growing up." In the process of evolution "we have lost our tails, we have not yet grown wings." "Vegetarianism is harmless enough though it is apt to fill a man with wind and self-righteousness." "The path of medical progress is strewn with the wrecks of discarded fads: bottles of soured milk, piles of special foods, innocent of the smallest trace of purins, broken electrical apparatus, innumerable tablets confidently recommended by many; there they all lie. And which of us can lay his hand on his heart and truthfully say he never used any of them?" "We are now realizing that a little reason mounts guard perilously and indecisively over a whole mass of emotions and instincts inherited from a far-distant past."

THE LIVER AND ITS DISEASE. Comprising the Lowell Lectures delivered at Boston, Massachusetts in March, 1947. *H. P. Himswoth, M.D.* Harvard University Press. Cambridge, Mass., 1947, pp. 204, price \$5.00.

This is an interesting little book full of interesting material, well written and well illustrated. There are good bibliographies attached to every chapter. Dr. Himswoth is Professor of Medicine at the University of London. He has done much research in this field and knows whereof he speaks. For all those workers in this field who would like to know what is being done in Great Britain, this book is ideal.

# ABSTRACTS OF CURRENT LITERATURE

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## MOUTH AND ESOPHAGUS

KAY, E. B. Surgical treatment of cardiospasm. *Ann. Surg.*, 127: 34 (Jan.) 1948. Seventeen patients with cardiospasm who had not been significantly improved by instrumental dilatation received transpleural cardioplasty. The technic provides for incising the diaphragmatic hiatus radially, excising any limiting bands about the esophago-gastric junction, pulling the cardia through the diaphragm, occluding the esophageal and gastric lumina, incising the esophago-gastric junction longitudinally for a distance of four inches and closing the opening by suturing it transversely. In each patient there was better relief of the dysphagia than had been obtained by previous measures, and spontaneous reduction in the radiographic size of the esophagus following operation.

LEMUEL C. McGEE.

## STOMACH

BOURNE, W. A. Cancer of the stomach in Addison's anaemia. *Brit. Med. J.*, 4541: 92 (Jan.) 1948. Examination of 15 symptom-free patients with pernicious anemia by X-ray and gas-

troscopy revealed cancer in 3. The patients, 2 males and 1 female, were more than 65 years of age and had been treated for at least 10 years. The carcinomas involved the lower third of the stomach. One case is of especial interest in that, despite suggestive roentgen evidence of an early scirrhous lesion in the prepyloric region, and fixation and absence of peristalsis at gastroscopy, operation apparently did not disclose evidence of neoplasm, though the stomach was not opened. Clinical symptoms of neoplasm appeared 18 months later, and operation at that time disclosed a large carcinoma of the pyloric end of the stomach.

JOSEPH B. KIRSNER.

GAILEY, A. A. H. Congenital hypertrophic pyloric stenosis. Report of four cases in brothers. *Brit. Med. J.*, 4541: 100 (Jan.) 1948.

The occurrence of congenital hypertrophic pyloric stenosis in four brothers is described, the second instance of this condition in four members of the same family to be reported. Rammstedt's operation was successfully performed in each case and convalescence was uneventful.

JOSEPH B. KIRSNER.

SWENSON, P. C. Mass survey of the gastrointestinal tract. *Southern Med. J.*, 41: 108 (Feb.) 1948.

The stomach is still the most common site of cancer in the human body. Uterine cancer is second, but causes only half the number of deaths that carcinoma of the stomach does. In the United States about 40,000 people die of gastric carcinoma each year, the death rate being about 30 in every 100,000 population.

The author discusses a recent statement by Kirklin and Hodgson to the effect that mass surveys for cancer are impractical. According to these workers, a mass survey of people over 40 years of age would necessitate the examination of 42 million people. It would take 1,900 radiologists, examining a stomach every 4 minutes for 8 hours each day, about a year to complete such a task. Since the examinations would have to be done every three months to catch lesions in their incipient stage, it has been estimated that it would require 7,150 radiologists to carry out the program. This is more than three times the number of active diplomates of the American Board of Radiology.

Swenson describes a method employed at the Detection Clinics of the Donner Foundation in Philadelphia. One anterior and two oblique exposures are made in the erect position. This method enables more than one radiologist to view the films, though the advantages of fluoroscopy are lost. It is too early to evaluate the results, since only about 500 patients have been examined with negative results. If such a method proves practical, Swenson believes that the enormity of the task should not be considered a deterrent.

ANTHONY M. KASICH.

EFSKIND, L. The problem of hypoproteinemia in delayed gastric emptying after stomach resection. *Acta Chir. Scand.*, 95: 81 (Jan.) 1947.

Patients with edema due to hypoproteinemia do not have a higher percentage of post-operative retention than patients without edema. The author does not believe that visceral edema is responsible for the delayed gastric motility after operation.

PHILIP LEVITSKY.

## BOWEL

SWENSEN, P. C. AND WIGH, R. The role of the roentgenologist in the diagnosis of polypoid disease of the colon. *Am. J. Roent. Rad. Therapy*, 59: 108 (Jan.) 1948.

On roentgenological examination, polypoid lesions of the colon are elusive. The first clue is obtained during the initial filling of the colon where the defect is seen. This is especially true before the walls of the colon are completely separated. When the colon is expanded the polyp may be completely hidden and it may again be observed on compressing the area. The polyp defect is brought out well by the spot pressure filming. The polyp may be movable if it has a pedicle and give the impression of fecal content. Occasionally one may visualize dimpling or puckering of the bowel wall at the site of attachment of the polypoid growth. The author emphasizes that the lesion must be reproduced and that no method is always infallible in demonstrating all the lesions. The differentiation between a benign polyp and a malignant polyp cannot be made. The size of a polyp is no accurate index of its histopathology.

A clinical grouping of the cases was found to be invaluable. Those with polypoid disease fall into 4 different groups: (1) patients suffering from hemorrhage from the bowel, the sigmoidoscopic examination revealing no lesion; (2) patients with bloody stools associated with a proved growth in the rectum; (3) patients which require an examination for exclusion of a lesion; and (4) clinical ulcerative colitis associated with polyposis. The authors present 10 illustrative cases roentgenologically demonstrating the polypoid lesions.

MAURICE FELDMAN.

LAUFMAN, H. AND METHOD, H. The role of vascular spasm in recovery of strangulated intestine. Experimental study. *Surg. Gyn. Obs.*, 85: 675 (Dec.) 1947.

This study concerns itself with two problems: (1) the development of a method of recognizing grossly the degree of vasospasm which might serve as an index to the recoverability of strangulated intestine, and (2) an evalua-

ation of present methods of resuscitation and an investigation into additional measures which could be of practical value. Vasospasm as one of the factors affecting the recoverability of strangulated intestine is of great significance, whether the strangulation be primarily arterial or venous. By obtaining intestinal surface temperature readings, an indication of residual vasospasm in the minute vessels of a still viable loop was observed. An important difference, however, in the gross appearance of the still viable arterial and venous type strangulation is that the former retains recoverability more than 5 times as long as the latter. In nonviable segments of either kind, release of strangulation results in a poor temperature response or an actual decline in temperature.

The use of papaverine hydrochloride for releasing residual vasospasm is discussed. When papaverine was given in large doses in addition to the accepted measures of oxygen inhalations, mesenteric novocaine injections and warm packs, an additional response was usually observed.

FRANCIS D. MURPHY.

SCHAFFNER, V. D. Intestinal tuberculosis. Can. Med. Assoc. J., 57: 561 (Dec.) 1947.

Intestinal tuberculosis, according to Schaffner, is a common disease in tuberculosis institutions. It is estimated that at least 90 per cent of far advanced, open cases, unfit for collapse therapy, have extensive tuberculous intestinal lesions. It occurs as a direct result of swallowed sputum. The initial lesions are found in the lymphoid patches of the gut and in the appendix. Constant abdominal pain in a patient with pulmonary tuberculosis is regarded as significant. When the lesion progresses to the sclerotic stage, the pain becomes cramping and spasmoid, and symptoms and signs of partial or complete bowel obstruction appear. The onset of diarrhea, intermittent or constant, also is important. The diagnosis is based on the clinical picture and on roentgen studies. The finding of tubercle bacilli in the stools is of little diagnostic value.

The first step in therapy is to control the

pulmonary disease, and to render the sputum negative. If bowel lesions do not heal with control of the pulmonary tuberculosis, it is felt that the intestinal lesion is best treated by resection rather than prolonged medical treatment, provided that the process is sufficiently localized. In a series of 109 consecutive cases operated upon for acute or subacute abdominal conditions, 101 suggested the diagnosis of acute appendicitis and 8 had evidence of obstructive lesions. Of the 101 with symptoms of appendicitis, 20 (19.8%) were found to have tuberculosis of the appendix or ileo-cecal region. The data on 25 cases are presented.

JOSEPH B. KIRSNER.

CAMPBELL, D. D. Carcinoma of the left colon. Can. Med. Assoc. J., 57: 537 (Dec.) 1947.

A brief discussion is presented on the diagnosis of carcinoma of the left colon with three case histories illustrating the value of repeated examination. Preoperative preparations, choice of anesthetic and selection of operation are considered. The author describes a new method of combined abdomino-perineal resection of the rectum and simultaneous dissection of the perineal and pelvic portion; the two dissections meet in the hollow of the sacrum. The operative time is less than one hour and shock is markedly reduced. The colostomy is covered by a simple pad and binder. Of 40 cases, 10 were found to be inoperable at laparotomy. There were 4 deaths from operation among the remaining 30.

JOSEPH B. KIRSNER.

HODGES, F. J., RUNDLES, R. W., AND HANELIN, J. Roentgenologic study of the small intestine. I. Neoplastic and inflammatory diseases. Radiol., 49: 587 (Nov.) 1947.

More and more, the importance of the roentgenological examination of the small intestine is recognized. The authors used the following method: after fluoroscopy and roentgenology of stomach and duodenum they took films 2½ and 5 hours after the barium meal. Several very interesting cases are reported. They include primary carcinoma of the jejunum, lymphoblastoma of the duodenum, regional jejunitis, peri-

appendiceal abscess, ulcerative ileocolitis, and ileocecal tuberculosis.

Of special interest is one case which was studied and treated intensively for a period of 8 months. At no time was there clinical evidence of specific vitamin deficiency, anemia, or neurologic disease. The roentgenograms showed abnormal dilatations and contractions of stomach, small and large intestines. The small intestine resembled those seen in severe vitamin deficiencies. There was no significant response to therapy. Death eventually occurred as a result of failure of the motor and absorptive functions of the intestinal tract. At necropsy there was extreme atrophy of all the organs, and muscular atrophy with diffuse fibrosis of the entire intestinal tract. Special examination of the central and peripheral nervous system demonstrated advanced myelin degeneration of the spinal cord and sciatic nerve. The ganglia of Auerbach's plexus were swollen, their neurons were reduced in number, and the perisomatic glia was proliferated. It is evident that both the central and the peripheral nervous system suffered damage to a degree which was no longer compatible with life, but one cannot be certain whether they were primary in origin, or secondary to some systemic disorder.

FRANZ J. LUST.

SPENCER, J. AND THAXTER, L. T. Acute obstruction of the small bowel. *Radiol.*, 49: 611 (Nov.) 1947.

It must be emphasized that there are a large number of cases presenting problems in the diagnosis of obstruction that will require frequent examination of the abdomen, including palpation and auscultation as well as repeated radiographic studies. The selection of cases that have been verified surgically necessarily limits the doubtful cases and allows for a more accurate correlation of the roentgen and operative findings. The radiographic findings were conclusive of obstruction in 94 per cent of the cases, and the level of obstruction can be localized roentgenographically. The mechanism of obstruction in 100 cases of small intestinal obstruction was analyzed and includes adhesions with and without pre-

vious laparotomy (79% of cases), hernia, intussusception, ileitis, Meckel's diverticulum, and gallstones.

FRANZ J. LUST.

INTERIM REPORT OF SURGICAL SUBCOMMITTEE OF THE CLINICAL RESEARCH COMMITTEE OF THE PUBLIC HEALTH DEPARTMENT OF THE LONDON COUNTY COUNCIL. Viability of strangulated bowel. *Brit. Med. J.*, 4540: 43 (Jan.) 1948.

Analysis of 336 cases, with particular reference to those features suggesting the ultimate fate of the strangulated bowel, indicated that the risk of subsequent gangrene increased with the length of bowel involved. No case was reported in which total gangrene of a segment of bowel occurred after replacement in the peritoneal cavity. Stenosis of the bowel with peritoneal adhesions supervened in two instances, suggesting that mucosal and perhaps peritoneal damage had occurred, and that the replaced bowel was on the borderline of viability. Among 216 "replacement" cases in which the bowel color was normal, the mortality was 9.7 per cent, as compared with 30 per cent among 20 instances in which the bowel was discolored. The presence of muscular contractions in the bowel and pulsations in the mesenteric vessels was associated with a more favorable prognosis.

The chief causes of strangulation, which excluded intussusception, were hernia, chiefly femoral and inguinal, (91.9%), bands or adhesions (6.0%), and volvulus (2.1%). Inguinal herniae tended to come to operation earlier than femoral herniae. There were 68 deaths—a total mortality of 20.2 per cent. The case fatality increased with the duration of strangulation. There was no statistical difference in death rate between patients undergoing resection and lateral anastomosis and those with resection and end-to-end anastomosis.

JOSEPH B. KIRSNER.

AULR, G. W. Surgical treatment of chronic ulcerative colitis. *Am. J. Surg.*, 75: 325 (Feb.) 1948.

It is probable that about 15 to 20 per cent of all cases of chronic ulcerative colitis reach an advanced stage. The objective of medical and surgical treatment should be a restoration to health and previous occupation. Surgery in the advanced process of ulcerative colitis was classified under specific and elective indications. Specific indications for surgery are (1) chronic ulcerative colitis with constitutional and visceral degenerative changes, (2) anorectal complications, (3) polypoid degeneration and carcinoma, (4) obstruction and tumor mass and (5) subacute perforation, abscess and fistula. Elective indications for surgical intervention include (1) focal infection, (2) hemorrhage, (3) acute fulminating ulcerative colitis, and (4) acute perforation.

The surgical procedures were planned to suit the requirements of the patient, and the following were applicable: (a) ileostomy without colectomy, (b) ileostomy with colectomy without resection of the rectum, (c) ileostomy with total colectomy and abdomino-perineal resection, (d) ileostomy and right colectomy, (e) left colectomy and abdomino-perineal resection, (f) ileosigmoidostomy with total colectomy, (g) segmental resection and anastomosis, (h) colostomy.

The analysis of operative procedures reveals that 20 patients underwent 35 operations with a postoperative mortality of 8.5 per cent. A restoration to health and previous occupation was accomplished for 70 per cent of the patients.

MICHAEL W. SHUTKIN.

#### LIVER AND GALL BLADDER

ST. JOHN, B. D. Jaundice and liver function tests. To what extent are they necessary? N. Y. State J. Med., 48: 75 (Jan.) 1948.

Jaundice is due to an excess amount of bilirubin in the blood, whether because of an increased production in the presence of normal excretion, or a normal production and diminished excretion. There are two types: obstructive and non-obstructive jaundice. The first type arises because of stones, tumors or inflammatory exudate within the common bile duct. It may also be due to extrinsic pressure. Non-obstructive jaun-

dice is either hemolytic in origin or toxic. The liver has numerous functions and each one requires a different test to disclose any disturbance in that function. In a case of suspected obstructive jaundice the most useful tests are urobilin in urine, bilirubin levels in the blood, serum alkaline phosphatase, and Hanger's cephalin flocculation test. The tests for nonobstructive jaundice are not very conclusive. The clinical investigation in a case of jaundice is more valuable than most liver function tests for determining whether one is dealing with surgical (obstructive) jaundice or medical (non-obstructive) jaundice.

PHILIP LEVITSKY.

KAPEL, O. Operative treatment of gallstone ileus without enterostomy. *Acta Chir. Scand.*, 95: 54 (Jan.) 1947.

Gallstone ileus is very difficult to diagnose clinically. It usually occurs in old women. A history of cholelithiasis may be present. In the author's two cases diagnosed preoperatively, laparotomy was performed and the stone was milked along the ileum through the ileocecal valve into the colon. Enterotomy was thus avoided, and the stones were passed spontaneously in both cases.

PHILIP LEVITSKY.

MORRISON, L. M. Types of cirrhosis of the liver responsive to treatment. *Rev. Gastroenterol.*, 15: 119 (Feb.) 1948.

The author divides cirrhosis into two classifications, the fatty and non-fatty types. The former, when advanced, is identical with portal or Laennec's cirrhosis, and is usually associated with excessive intake of alcohol and nutritional deficiency. The latter includes the hypertrophic biliary cirrhosis of Hanot or the cholangiolitis cirrhosis. Diagnoses were made by liver biopsy.

Seventy patients with cirrhosis were treated by a high protein (high carbohydrate) low fat diet; liver extract; vitamins; and choline. Twenty-three patients were treated by paracentesis, diuresis, and high carbohydrate diet. The author designates the former group as "untreated". After 2 years, all patients in the treated group without ascites were alive as compared with

27 per cent mortality rate in the control series. Sixty-two per cent of the treated patients without ascites had returned to normal activity in 2 years as compared to 18 per cent of the control group. Thirty-four per cent of the treated patients with ascites had returned to normal activity in two years as compared with 17 per cent of such patients in the control series.

C. WILMER WIRTS, JR.

SHAY, H. AND SIPLET, H. Minimal yet adequate program of liver function studies in the differential diagnosis of jaundice.

Am. J. Med., 4: 215 (Feb.) 1948.

Congenital or acquired hemolytic icterus is characterized by splenomegaly, reticulocytosis, spherocytosis, increased fragility, urobilinogenuria, and hyperbilirubinemia. The diagnosis of hepatocellular and obstructive jaundice is often impossible despite a careful history and exhaustive physical examination. Liver functions may contribute valuable aid to the ultimate diagnosis but the number of tests are best limited to an adequate minimum. In addition to a reliable method for measuring the degree of icterus, the plan should include at least two tests which give positive results in obstructive jaundice and two whose results are positive in hepatocellular jaundice. Liver function tests should be done early and repeated at short intervals.

The minimum tests recommended for the differential diagnosis of obstructive and hepatocellular jaundice are: (1) quantitative van den Bergh, (2) serum cholesterol partition, (3) serum alkaline phosphatase, and (4) thymol turbidity. Where laboratory facilities are limited, jaundice may be followed by combining the (1) methylene blue test, (2) the galactose tolerance test, and (3) the thymol turbidity. If such studies are continued at 4-7 day intervals, a sounder prognosis is possible than that gleaned from clinical observation alone. The investigator may thus take due cognizance of the multiplicity of liver functions, the "dissociation" of the effects of liver damage upon these functions and the dynamic quality of liver function, inadequate appreciation of which has led to so much unjustified criticism of liver function tests.

Attempted evaluation of an isolated liver function test in jaundice is without meaning.

MICHAEL W. SHUTKIN.

ALTHAUSEN, T. L. Liver function tests in the differential diagnosis of jaundice.

Am. J. Med., 4: 208 (Feb.) 1948.

The present paper is devoted to a discussion of the value of various laboratory tests in the differential diagnosis of jaundice, and contains an analysis of 190 cases in which the diagnosis was definitely established by operation, autopsy or clinical course. In the differential diagnosis of jaundice, liver function tests are important but they do not replace a good history and physical examination. Ordinary laboratory studies are helpful in ruling out hemolytic jaundice. Among the metabolic functions of the liver most decisive for the differentiation of obstructive and parenchymatous jaundice is the ability of the liver to metabolize galactose, and produce prothrombin following an injection of vitamin K. Every patient with jaundice should have an intravenous galactose test and a test for the prothrombin response to vitamin K. It is very important to distinguish obstructive jaundice which requires surgical interference from parenchymatous jaundice which is strictly a medical problem.

MICHAEL W. SHUTKIN.

KUNKEL, H. G. Value and limitations of the thymol turbidity test as an index of liver disease. Am. J. Med., 4: 201 (Feb.) 1948.

The purpose of this report is to present certain clinical observations on the value and limitations of the thymol turbidity test and to attempt to explain the results in 76 patients with infectious hepatitis in terms of maximal aberrations. In infectious hepatitis and acute liver disease, a positive reaction occurs although the degree of turbidity is not a reflection of the severity of the liver damage. In mild non-icteric cases of infectious hepatitis, the thymol turbidity test was found to be a more sensitive indicator of the presence of the disease than any other test that could be applied. It will remain positive for at least six weeks enabling one to make the diagnosis several weeks after all other clinical and laboratory

indications of the disease had disappeared. It is a useful test in anticipating relapses of infectious hepatitis and in the evaluation of mild, persistent symptoms following an attack of this disease. In cirrhosis of the liver, values for the thymol turbidity test proved to be considerably more variable than in infectious hepatitis. High values were found to be associated with the hyperglobulinemia found in kala azar, malaria and typhus. In certain chronic disease such as rheumatoid arthritis and multiple myeloma, values for the reaction did not correspond to the marked hyperglobulinemia that was present in some of these patients. The thymol turbidity test alone may be of considerable value in differentiating between obstructive and non-obstructive jaundice especially when combined with the alkaline phosphatase, cephalin flocculation and serum bilirubin determinations. It may distinguish between infectious hepatitis and familial hemolytic jaundice. Although there is a close relationship in the reactions of the thymol turbidity test and cephalin flocculation, in infectious hepatitis the latter test became positive several days earlier than did the thymol turbidity reaction and is thus considered more useful during the pre-icteric stage.

MICHAEL W. SHUTKIN.

#### PANCREAS

ELIASON, E. L. AND WELTY, R. F. Pancreatic calculi. *Ann. Surg.*, 127: 150 (Jan.) 1948.

At autopsy pancreatic calculi are found in the ratio of 1 in 1,500-3,000 cases. From reviewing abdominal X-ray films the incidence has been reported as 1 in 754 cases. In a series where the pancreas was removed at autopsy and examined roentgenologically, calcification was found in 1 of every 20 specimens. Calculous disease of the pancreas predominates in the male in the ratio of 3 or 4 to 1, and is found most commonly in the 4th and 5th decades of life. Thirty to forty per cent of these patients have diabetes mellitus.

There may be no symptoms. The commonest symptom is pain of the epigastric colic type. There may be weight loss; vomiting; bulky, frothy, fatty stools; and

associated biliary tract disease. Complications include hemorrhage and the development of cysts, abscesses, and carcinoma. The mortality rate for operative treatment of pancreatic calculi is about 18 per cent. Nine cases with pancreatic calculi receiving surgery are reported briefly. One patient died, one other was not imporved, and the remaining seven patients were relieved.

LEMUEL C. McGEE.

JEMERIN, E. E. AND SAMUELS, N. A. Cystadenoma of the pancreas. *Ann. Surg.*, 127: 158 (Jan.) 1948.

Cystadenoma of the pancreas is an uncommon disease. Its incidence is not established because of difficulty in its separation from cysts due to defective pancreatic development. The lesion is most likely to be found in the tail of the pancreas. It is more common in females than in males. The symptomatology is that expected of a slowly expanding lesion in this location: pain, epigastric discomfort after meals, belching, nausea and vomiting. Roentgenograms help in the diagnosis by showing compression defects in the stomach, duodenum or transverse colon. Whereas marsupialization is the common method of surgical treatment in other varieties of pancreatic cyst, cystadenomas should be dissected out. Often a cleavage plane can be found.

A case is reported wherein there was successful removal of a cystadenoma from the head of the pancreas in a 31-year old female. Before operation a slightly irregular firm mass about the size of a tangerine was palpable in the mid-epigastrium. It was freely movable. The specimen after removal was a nodular, globular mass about 10 cm. in diameter. The individual cysts were from 0.25 to 1.0 cm. across and were lined by epithelial cells which varied from cuboidal to flat.

LEMUEL C. McGEE.

PESSAGNO, D. J. AND SCHAEFER, J. F. Pancreatic cysts—with report of two cases.

*Southern Med. J.*, 41: 166 (Feb.) 1948.

Pancreatic cysts are rare lesions. Only nine cases were reported from the Lahey Clinic from 1926 to 1945. Any fluid tumor in or associated with the pancreas can be

described as a cyst. It can arise wholly within the pancreas. There are several types of true pancreatic cyst: the proliferative cyst (cystic adenoma or cystic adenocarcinoma); the degenerative cyst, resulting from softening and cystic degeneration due to necrosis; the retention cyst, from mechanical blockage of the pancreatic duct; the echinococcus cyst; the congenital type, associated with cysts of the liver and kidneys; the hydatid cyst; and the cystic dermoid.

Another form of cyst is actually an effusion into the lesser peritoneal cavity. Because of its close proximity to the pancreas, it is called a peripancreatic cyst or pseudocyst. This cyst never originates from the gland substance. It is generally caused by trauma to the upper abdomen, or arises as a sequel to an acute or chronic pancreatitis which, by a process of contiguous inflammation, initiates the effusion into the lesser peritoneal sac. Differentiation between true and pseudocysts is seldom made during life.

Cysts vary in size from a small tumor of primary pancreatic degeneration to huge masses. They are usually round or oval, smooth, fluctuating masses in the epigastrium. They are generally in the midline although they may be located beneath the lip or, more rarely, beneath the right costal margin. Signs of pancreatic insufficiency may be present. The most prominent symptom is pain. Epigastric fullness, flatulence, loss of weight and vomiting are frequently seen. Pancreatic cyst must be differentiated from mesenteric cyst, tumors of the ovary, omental cysts, adrenal cysts and renal cysts. Treatment is surgical, marsupialization being the most common and successful operation.

ANTHONY M. KASICH.

HARPER, A. A. AND MACKAY, I. F. S. The effects of pancreozymin and of vagal nerve stimulation upon the histological appearance of the pancreas. *J. Physiol.*, 107: 89 (Jan.) 1948.

The effects of secretin, pancreozymin and vagal stimulation upon the zymogen granule content of the cat pancreas were studied together with the enzyme output in the

juice. Secretin produced the secretion of juice of a low enzyme content and did not affect the granule content of the cells. Stimulation of the dorsal vagal trunk and the administration of pancreozymin each resulted in an increased output of enzymes in the juice and diminution in the granules in the cells. The increased enzyme output in response to repeated doses of pancreozymin was maintained for periods up to 3½ hours. The increased output of enzymes in the juice, and the alterations in the histological appearance of the pancreas in response to pancreozymin are not affected by injection of atropine which abolishes the effect of vagal stimulation.

ALBERT CORNELL.

MAIMON, S. N., KIRSNER, J. B., AND PALMER W. L. Chronic recurrent pancreatitis. A clinical review of twenty cases. *Arch. Int. Med.*, 81: 56 (Jan.) 1948.

The authors studied 20 patients with chronic pancreatitis. Twelve were men and 8 were women. In 60 per cent of the cases, the average duration of symptoms was four years. In 85 per cent, the chief complaint was recurrent severe pain in the upper abdominal area. Jaundice of varying degree was present in 25 per cent. The oral glucose tolerance test showed a diabetic type of curve in 8 out of 9 patients and a flat curve in the ninth. Disturbances of carbohydrate metabolism were present in 10 of the 20 patients. Seven of these had diabetes and 3 had transitory glycosuria. Steatorrhea was present in 5 cases and pancreatic calcifications in 7. The possibility of recurrent pancreatitis should be considered especially in cases in which the patient continues to have attacks of pain simulating that of biliary colic after cholecystectomy has been performed.

EDGAR WAYBURN.

PAXTON, J. R. AND PAYNE, J. H. Acute pancreatitis. *Surg. Gyn. Obs.*, 86: 69 (Jan.) 1948.

This paper is a review of 307 patients admitted to the Los Angeles County General Hospital from January 1933 to January 1946 with the diagnosis of acute pancreatitis. From a clinical standpoint, the disease

usually falls into one of 5 groups: (1) the standard textbook description of acute pancreatitis, (2) acute cholecystitis, (3) mechanical small intestinal obstruction, (4) acute alcoholism with acute gastritis, and (5) cases with a mass either in the epigastrium or the left upper quadrant. Other symptoms associated with the above, such as gastrointestinal hemorrhage, diarrhea, and hypertension are discussed.

Diagnosis is dependent on the following laboratory aids: (1) elevated blood amylase, (2) elevated blood sugar, (3) depressed blood calcium, (4) elevated urinary diastase, (5) glycosuria, (6) roentgenogram of the abdomen, and (7) changes in the electrocardiogram. Conservative treatment is recommended because of the results obtained. Premature discontinuation of active therapy will result in reactivation of the disease. There was an overall mortality of 33.3 per cent in this series.

FRANCIS D. MURPHY.

#### ANEMIAS

LANDBOE-CHRISTENSEN, E. AND PLUM, C. M. Experimental study on the localization of Castle's intrinsic factor in the human stomach. *Am. J. Med. Sci.*, 215: 17 (Jan.) 1948.

It has been reported that the pyloric portion of the hog stomach contains the antipernicious anemia factor whereas the fundal portion has little or no activity. The authors separated, dried and powdered the pyloric and fundal portions of human stomach obtained at autopsy. Feeding the fundal part to a patient with pernicious anemia over a period of 8 days produced a striking hematologic response. This confirms the previous finding of Fox and Castle. Feeding the pyloric portion of the human stomach to a similar patient produced only a moderate therapeutic effect. This finding is consistent with the observation that the fundal portion of the human stomach undergoes the more conspicuous histologic changes in pernicious anemia.

LEMUEL C. McGEE.

#### ULCER

GORDON, A. H. The treatment of peptic ulcer. *Can. Med. Assoc. J.*, 58: 38 (Jan.) 1948.

The author briefly reviews the important clinical features and complications of peptic ulcer. Therapy is directed to the control of hyperacidity, infection, pylorospasm and hypermotility, by means of diet, rest, education and surgery. The inadvisability of an operation for a presumptive ulcer unsupported by roentgen evidence of a crater or deformity, is properly emphasized.

JOSEPH B. KIRSNER.

BALL, R. P., SEGAL, A. L. AND GOLDEN, R. Post-bulbar ulcer of the duodenum. *Am. J. Roent. Rad. Therapy*, 59: 90 (Jan.) 1948.

The actual incidence of post-bulbar ulcers of the duodenum is not established. The reported roentgeological incidence is low. An ulcer crater located in the duodenum distal to the apex of the bulb is classified as a post-bulbar ulcer; these ulcers are seen best in exaggerated oblique views. The most characteristic roentgenographic sign is an indentation of the wall of the duodenum at the site of the crater, presumably due to spasm. The ulcer crater is usually seen on the mesial side of the descending duodenum. The post-bulbar ulcer may be associated with a bulbar ulcer; this occurred in one of the authors' series. Irritability of the proximal duodenum and of the bulb was present in all cases. Enlargement of the mucosal folds and loss of usual markings of the mucosa was constant. Post-bulbar ulcers are differentiated from duodenitis, diverticula, neoplasms and other lesions.

MAURICE FELDMAN.

BINGHAM, D. L. C. The treatment of acute perforated peptic ulcer. *Can. Med. Assoc. J.*, 58: 1 (Jan.) 1948.

Conservative treatment of perforated peptic ulcer is indicated, according to the author, in the following instances: (1) cases in which the perforation is of less than 8 hours' duration, (2) cases in which perforation takes place more than 1 hour after the last large meal, (3) cases in which, as judged by the previous history, the perforated ulcer is duodenal rather than gastric, (4) cases in which perforation, as judged by the clinical picture, is probably very small, (5) late cases with perforation of more than 3 days' duration, and (6) cases in which it has been

impossible at first to distinguish clearly between perforation and other less serious upper abdominal catastrophe. Recovery occurred in all of 5 patients treated conservatively.

The operative treatment of perforated peptic ulcer is indicated in: (1) perforations of more than eight hours' duration, (2) perforation occurring less than one hour after the last large meal, (3) patients which have drunk a large quantity of fluid just before or after the moment of perforation, (4) patients with known pyloric stenosis and gastric dilatation, (5) cases in which the perforated ulcer is in all probability malignant, and (6) late cases requiring surgical drainage of an intraperitoneal abscess. The recommended operation is simple suture of the perforation generally without drainage of the peritoneal cavity.

JOSEPH B. KIRSNER,

PRICE, P. B. Repair in the normal and hyperacid stomach. An experimental study. *Surg. Gyn. Obs.*, 86: 59 (Jan.) 9184.

A large number of healthy dogs were used in this study to observe the process of healing of wounds and incisions in the normal and hyperacid stomach. About one-half of the animals received daily intramuscular injections of histamine in beeswax beginning 24 hours after operation. The other group received no histamine. In approximately 100 normal dogs, no spontaneous ulcers were observed. However, in dogs with hyperacidity, spontaneous ulcers, artificial defects, and sutured incisions all showed inflammation, necrosis, and autodigestion. These 2 conditions, normal repair and hyperacidity, could be made to change from one to the other by giving or withdrawing histamine. It is suggested that these observations may help to explain the healing or persistence of peptic ulcers.

FRANCIS D. MURPHY.

LEVEEN, H. H. The effect of surgical interruption of the gastric blood flow upon gastric secretion and the prevention of experimental peptic ulcers. *Surg. Gyn. Obs.*, 86: 164 (Feb.) 1948.

By a reduction of the hydrochloric acid secreted by the stomach through ligation

of the major gastric vessels, it was shown that dogs are protected from development of typical peptic ulcers induced by intramuscular injections of histamine in beeswax. Vascular ulcers on the midportion of the greater curvature of the stomach may be produced, however, by too extensive a ligation. By determining the extent of ligation necessary, vascular ulcers may be avoided.

FRANCIS D. MURPHY.

#### PROCTOLOGY

GRANET, E. Is anal fistula a necessary sequel to perianal abscess? *N. Y. State J. Med.*, 48: 63 (Jan.) 1948.

Perianal abscesses should be incised early and widely. It is important to locate the internal infected focus in the anal crypt, duct or intramuscular gland, and to excise it. In 43 patients with infralevator abscesses operated on by the author, the "stem to stern" operation resulted in healing in 93 per cent.

PHILIP LEVITSKY.

KOCH, F. A contribution to the operative treatment (resection) of cancer of the rectum. *Acta. Chir. Scand.*, 95: 145 (Jan.) 1947.

In an analysis of 276 cases of cancer of the rectum, an association between this disease and hemorrhoids was found in 9 per cent of the patients. Fifty-five per cent of the 276 cases were found to be operable when first seen. In 66 cases, the growth was high enough to permit resection with retention of the anal sphincter.

PHILIP LEVITSKY.

SELETZ, R. Rationale of therapy in pruritis ani. *Am. J. Surg.*, 75: 313 (Feb.) 1948.

The rationale in the treatment of pruritus ani involves its recognition as a syndrome plus the associated symptoms of anospasm, insomnia, nervous depression, poor peripheral circulation, excessive perspiration, a moderate leukopenia, and a subclinical nutritional state. The nervous manifestations represent a vagosympathetic imbalance of the vagotonic type. Therapeutic measures such as bromides, barbiturates and anti-histamine drugs that tend to calm the psychic state or reduce nervous irritability,

become valuable factors in the treatment of the pruritus. Deficiency of vitamin B complex may be a strong element in the symptom-complex.

The basic pathologic condition consists of three factors: skin irritation, anospasm and lymph edema. Together they constitute both the cause and effect of neurovegetative imbalance and form the ground-work of this syndrome. The injection methods produce a phagocytic response which removes or reduces the congestion in the peripheral circulation. Anal spasm due to rectal pathology requires a cautious surgical therapeutic approach of the organic lesion. The excessive perspiration of the apocrine sweat glands affords a favorable site of predilection for the cultivation of fungi. Fungicidal ointments owe their effectiveness to their acid nature but must be chosen individually. In special instances it is best to use penetrating dyes and give all features of the syndrome equal respect.

MICHAEL W. SHUTKIN.

FRANKFELDT, F. M. Pyribenzamine—its role in the treatment of pruritis ani.

Am. J. Surg., 75: 307 (Feb.) 1948.

Pruritus ani is an allergic phenomenon in which sensitization of the skin and an antigen operate simultaneously. A comprehensive history with intimate study of the involved integument supplemented by skin tests, will determine to what group the exciting allergen belongs.

Pyribenzamine is an anti-histamine agent which acts better prophylactically than correctively. The best therapeutic results were obtained in pruritus ani by the oral and local use of pyribenzamine. Additional instructions included the omission of condiments in the diet, local anal hygiene and ice packs, shower baths only, treatment of interdigital epidermophytosis, adequate protection and drainage of the skin, and the correction of constitutional and deficiency disease. Of the 90 patients treated with pyribenzamine, 57 had satisfactory results, and pruritus ani was controlled in 85-100 per cent of the cases. However, the fact that a considerable percentage of patients do not respond to pyribenzamine does not rule out the allergic origin of this disease.

Pyribenzamine will not cure this syndrome but it nevertheless merits a definite and important role in its treatment.

MICHAEL W. SHUTKIN.

COLVERT, J. R. AND BROWN, C. H. Rectal polyps: Diagnosis, 5 year follow-up, and relation to carcinoma of the rectum.

Am. J. Med. Sci., 215: 24 (Jan.) 1948.

This report concerns 235 instances of rectal polyps found in routine proctoscopic examinations. Symptoms were rare. Only 21 (8.9%) complained of rectal bleeding, only 9 (4%) complained of rectal discomfort. In 186 examinations for occult blood only 62 were positive. Anemia was uncommon.

Of polyps removed in 167 patients only 10 showed good evidence of malignancy (usually low grade). Of the benign polyps removed only 5 per cent were ulcerated whereas 37.5 per cent of the malignant polyps were ulcerated. Of the patients with benign polyps which were removed, 117 could be followed for 5 or more years. Only 3 patients (2.5%) developed carcinoma of the rectum during this period. Of patients who refused removal of the polyps 6.9 per cent developed carcinoma of the rectum within a comparable period. This figure is close to the figure of 5.9 per cent for malignancy found in rectal polyps on the first examination.

LEMUEL C. McGEE.

BACON, H. E. AND SMITH, C. H. The arterial supply of the distal colon pertinent to abdominoperineal proctosigmoidectomy, with preservation of the sphincter mechanism. Ann. Surg., 127: 28 (Jan.) 1948.

The authors review the literature describing the arterial pattern of the terminal colon and add observations of their own based on a study of the vascular supply of the colon and rectum in 71 cadavers and 264 operated patients. It was found that ligation of the inferior mesenteric artery must be performed above the lowest sigmoidal artery to permit bringing the colon well into the anus. The middle colic artery maintains the viability of the terminal colon in this technic for abdominoperineal proctosig-

moidectomy without colostomy and with preservation of the anal sphincter mechanism.

LEMUEL C. McGEE.

GREEN, W. W. Evaluation of the roentgenologic diagnosis of lesions of the rectum and sigmoid. *Am. J. Surg.*, 75: 348 (Feb.) 1948.

Cooperation between proctologist and roentgenologist is necessary in attaining an accurate diagnosis in a small group of cases. The superiority of the air-contrast enema over the routine barium enema demands its greater application in difficult diagnosis. In congenital malformations the X-ray can frequently contribute valuable preoperative information about the anus and rectum. Another useful procedure is the use of the Wangensteen-Rice maneuver for determining the distance of the blind sac from the perineum in a newborn infant with an imperforate anus and no demonstrable outlet.

Roentgen studies are of great value in the diagnosis of lesions above the lower sigmoid and in complicated fistulas. However, X-ray diagnosis may be erroneous and depend upon sigmoidoscopy for the correct diagnosis. Several case reports and illustrations exemplify the author's convictions.

MICHAEL W. SHUTKIN.

## SURGERY

HINTON, J. W. AND LOCALIO, S. A. One-stage resection and anastomosis of the colon. *Ann. Surg.*, 127: 12 (Jan.) 1948. Much of the surgery on the colon is now done by a one-stage resection and anastomosis. Such is the preference of the authors. It is noted that some 250 methods of anastomosis have been reported. Of these, about 45 are aseptic or nearly aseptic. The authors use an aseptic method employing the McClure modification of the Furness clamp. The details of the surgical technic for both the right and left halves of the colon are described and illustrated. In 26 consecutive colonic resections using this technic there was but one death which was due to a pulmonary embolus on the fifth postoperative day.

LEMUEL C. McGEE.

BEST, R. R. Selection of operative procedure to avoid colostomy in carcinoma of rectum and rectosigmoid. *Surg. Gyn. Obs.*, 86: 98 (Jan.) 1948.

This report deals with the choice of an operative procedure to avoid colostomy in selected cases of carcinoma of the rectum and rectosigmoid. Three types of operative procedures were proposed to permit sphincter preservation. These were abdominal dissection, resection and anastomosis; abdominal dissection with perineal resection and anastomosis; and perineal dissection with perineal resection and anastomosis. These types were discussed with their indications and limitations. Definite conclusions on the end results can be drawn only after a 5-10 year postoperative survey.

FRANCIS D. MURPHY.

BLACK, B. M. AND McEACHERN, C. G. Redundant blind segments of intestine following side-to-side anastomosis with division of the bowel. *Surg. Gyn. Obs.*, 86: 177 (Feb.) 1948.

There is little doubt that potential hazards associated with the closed end of the proximal segment of bowel are inherent in the operation of side-to-side anastomosis after division or resection of the bowel, since dilatation and hypertrophy, ulceration, and perforation may develop. When unusually long lengths of the proximal segment are left distal to the anastomosis, symptoms suggestive of partial obstruction may develop. The colicky pains occur in attacks and may be accompanied by vomiting and diarrhea. As was judged by the rarity of reported cases and the 5 cases in this series, it was evident that complications associated with the inverted proximal loop are successfully avoided in the great majority of cases and do not detract from the usefulness of side-to-side anastomosis.

FRANCIS D. MURPHY.

## PHYSIOLOGY: ABSORPTION

FOURMAN, L. P. R. AND SPRAY, G. H. Absorption of vitamin D in steatorrhoea. *Brit. Med. J.*, 4542: 142 (Jan.) 1948. Osteomalacia secondary to steatorrhea in a 61 year-old female is described. The

bone disease progressed despite treatment with a low fat diet and vitamin D and calcium supplements. On a daily intake of 70 g. of fat, 4.6 g. of calcium, and 12,000 i. u. of vitamin D orally, the patient retained 1.9 g. of calcium in 16 days. With the same doses of vitamin given intramuscularly, she retained 6 g. of calcium in 16 days. Apparently a failure to absorb vitamin D occurs in osteomalacia due to steatorrhea. Ten weeks after the conclusion of the experiment, blood calcium and phosphate levels had risen to normal with continued parenteral vitamin D therapy, but the phosphatase remained high.

JOSEPH B KIRSNER.

#### PHARMACOLOGY

ANGELO, G. Sulfathalidine in intestinal disease. A report of 587 proctologic cases. *Rev. Gastroenterol.*, 15: 145 (Feb.) 1948.

Sulfathalidine, sulfasuxidine, sulfaguanidine and sulfacarboxythiazole are the sulfonamides of choice in treating intestinal disease because a high concentration can be obtained in the intestinal tract with negligible absorption into the blood stream. Further study is required to evaluate sulfacarboxythiazole. Sulfaguanadine is often too readily absorbed while the effectiveness of sulfasuxidine is interfered with by the presence of liquid petrolatum, a hard or watery stool, or extensive ulcerative lesions. Sulfathalidine is considered the most satisfactory drug of this group and was therefore employed in 542 patients undergoing anorectal or bowel surgery and in 45 patients for medical treatment. Three to 5 grams was used initially and the same amount given daily in 3 divided doses. Toxic reactions were rare and peritonitis did not occur postoperatively. Distention and discomfort after operation was minimal and spontaneous bowel movements occurred early. In the unoperated patients, this drug was of material benefit in the treatment of diverticulitis; it relieved diarrhea, cramps, and prolonged remissions.

C. WILMER WIRTS, JR.

#### ANATOMY

DOUBILET, H., SHAFIROFF, B. G. P., AND MULHOLLAND, J. H. The anatomy of the peri-esophageal vagi. *Ann. Surg.*, 127: 128 (Jan.) 1948.

The authors report a study of the anatomy of the peri-esophageal vagus nerves in 32 cadavers. A variable number of fibers form the infra-aortic right and left vagal trunks, there is a variable peri-esophageal plexus and an inconstant number of separate fibers which pass through the esophageal hiatus. Four general types of anatomic arrangement about the esophagus are described: (1) the right and left vagus nerves communicate through fibers anterior to the esophagus, (2) there are no demonstrable communicationg fibers, (3) the communicating fibers are all posterior to the esophagus, and (4) the communicating fibers are both anterior and posterior to the esophagus. The nerves may pass through the esophageal hiatus as 2 or 3 branches both anteriorly and posteriorly.

LEMUEL C. McGEE.

SHAPIRO, A. L. AND ROBILLARD, G. L. The arterial blood supply of the common and hepatic bile ducts with reference to the problems of common duct injury and repair. *Surgery*, 23: 1 (Jan.) 1948.

In a study of injected cadavers it was found that the principal arterial branches for the common and hepatic ducts were derived from the cystic and posterosuperior pancreaticoduodenal arteries rather than from the hepatic artery. Some of the small branches act as end arteries and there is not marked circumferential anastomosis. Since the hepatic and common ducts in a rudimentary fashion resemble small intestine in structure, devascularization may be followed by ischemic necrosis, obliterative fibrosis, rupture, fistula formation, and failure of reconstructive ductal anastamosis. It is, therefore, recommended that minimal stripping of the common duct, especially on its medial border, should be employed for surface exposures.

J. DUFFY HANCOCK.

# American Gastroenterological Association CONSTITUTION AND BY-LAWS\*

## CONSTITUTION

### ARTICLE I

#### *Name*

The name of this Corporation is the American Gastroenterological Association, Inc.

### ARTICLE II

The American Gastroenterological Association is incorporated under the laws of the State of Delaware. The location of the corporate office is 311 South State Street in the city of Dover, county of Kent, Delaware. The name of the agent therein and in charge thereof is Arley B. Magee, Inc.

### ARTICLE III

#### *Objects and Purposes*

Section 1. To study the normal and abnormal conditions of the digestive organs and problems connected with metabolism, and to conduct scientific research and investigation related to or connected with the digestive organs and the problems connected with metabolism.

Section 2. To solicit and receive donations and to receive, manage, invest, and reinvest and hold real and personal property, to be used and applied for the purposes of such study, scientific research and investigation, the property so received to be accumulated or applied to the payment of salaries to research workers, purchase of materials, supplies and instruments or in any manner whatsoever for the objects and purposes above stated.

### ARTICLE IV

#### *Powers*

Section 1. Acting through its Governing Board, consisting of its officers and its Councilors, subject to the powers and restrictions of its certificate of incorporation, and its Bylaws, the American Gastroenterological Association is empowered to do all and only such acts as are necessary or convenient to the objects and purposes herein set forth, and to the same extent and as fully as any natural person might or could do; to purchase, lease, hold, sell, mortgage, or otherwise acquire or dispose of real or personal property; to enter into, make

\* As amended to May, 1948.

perform or carry out contracts with any firm, person, corporation or association; to do any acts necessary or expedient for carrying on any or all of the objects or purposes of the corporation not forbidden by the certificate of incorporation, or its Bylaws, or by the laws of the State of Delaware; to have offices and promote and carry on its objects and purposes within or without the State of Delaware, in other States, the District of Columbia, the territories and colonies of the United States, in Canada or elsewhere.

Section 2. The private property of the members shall not be subject to the payment of corporate debts to any extent whatever.

Section 3. The corporation shall have no capital stock and is not organized for profit.

Section 4. The American Gastroenterological Association, Inc. shall vest its general management in a Governing Board, consisting of its Officers and Councilors.

Section 5. The existence of this Corporation is to be perpetual.

## ARTICLE V

### *Membership*

Section 1. The American Gastroenterological Association, Inc. shall consist of Senior and Active members. The Association may also elect Associate and Honorary members, who, however, shall not be members of the corporation nor have the right to vote.

Section 2. The conditions of membership shall be as stated in the Bylaws of the Corporation.

## ARTICLE VI

### *Resignations and Expulsions*

Section 1. This Association adopts the Code of Ethics of the American Medical Association. The Governing Board shall promptly investigate any charges of unprofessional or unbecoming conduct made against any member and may initiate such investigation on its own account, but in every case the accused member must be informed of the charges and shall have the right to be heard in his own defense. The Governing Board shall report its findings and recommendations to the next annual meeting. If a member be found guilty by the Governing Board he may be expelled by an affirmative vote of three-fourths of the Senior and Active members present at the executive session of the annual meeting.

Section 2. A member may resign at any time by filing his written resignation with the Secretary, but such resignation shall not exempt him from the payment of dues for the year.

Section 3. Any member failing to attend three consecutive annual meetings of the Association without excuse acceptable to the Governing Board, may be dropped from the Association by vote of the Governing Board, but before he shall be dropped, notice must be sent him informing him of the proposed action.

Section 4. Any member whose dues are two years in arrears shall be dropped from the Association but on vote of the Governing Board he may be reinstated if all arrears are made up before the next annual meeting.

## ARTICLE VII

### *Quorum*

A quorum for the election of officers and members of the Governing Board, amendments to the Constitution, expulsions, or other business shall consist of at least twenty Senior or Active members present. For the reading of papers and discussions, any number of any class of members present shall constitute a quorum.

## ARTICLE VIII

### *Amendments*

Section 1. Proposed amendments to this Constitution shall first be submitted to the Governing Board for its recommendations. The recommendations of the Governing Board shall then be presented to the members of the Association for their consideration at least thirty days before the annual meeting either through the official publications of the Association or by letter. A three-fourths vote of the Senior and Active members voting at an annual meeting shall be necessary to adopt an amendment.

Section 2. Five Senior or Active members, either or both, may propose in writing an amendment at any annual meeting and such proposed amendment shall be acted upon at the succeeding annual meeting, the notices for which must contain a copy of the proposed amendment and the recommendations of the Governing Board as to its adoption or rejection.

## BYLAWS

### ARTICLE I

#### *Officers*

The officers of the American Gastroenterological Association, Inc. shall be a President, two Vice-Presidents, a Secretary, a Treasurer and a Recorder,

all to be elected annually by ballot at the executive session of the annual meeting of the Association, to hold office for the ensuing year and until their successors are elected.

## ARTICLE II

### *Councilors*

There shall also be three Councilors elected from the membership for a term of three years, except that at the first meeting one member shall be elected for one year, one member for two years and one member for three years, so that there shall be but one vacancy to be filled at each subsequent meeting.

## ARTICLE III

### *Governing Board*

The officers and the Councilors, collectively, shall become the Governing Board of the Association and the general management of the Association shall be vested in said Governing Board.

## ARTICLE IV

### *Admissions Committee*

There shall also be a Committee on Admissions consisting of three members elected for a term of three years, except that at the first meeting one member shall be elected for one year, one member for two years and one member for three years, so that there shall be but one vacancy to be filled at each subsequent annual meeting.

## ARTICLE V

### *Membership*

Section 1. The Association shall consist of Senior, Active, Associate and Honorary members.

Section 2. Senior members shall have all of the privileges of Active members, but they shall not be required to pay dues or to attend annual meetings. Any active member who has attained the age of sixty years and who is not in arrears in his dues, upon application to the Secretary, may at the discretion of the Governing Board be made a Senior member; and any Active member attaining the age of sixty-five shall without application be automatically transferred to this class, provided that he is not in arrears in his dues.

Section 3. Active members of the Association shall be limited to American (citizens of North, Central and South America) investigators, research workers and practitioners of medicine and surgery, of high moral standing, who have

attained eminence in their work on subjects pertaining to the digestive system or on problems pertaining to metabolism and nutrition.

Section 4. Associate members shall be elected for a period of not more than five years and should possess such qualifications as to give promise of sufficient development within that period, for advancement to Active membership. Associate members shall enjoy all the privileges of the Association with the exception of holding office, of having a vote and attending the executive session of the annual meeting.

Section 5. Honorary membership shall be restricted to physicians, surgeons and scientists who have attained pre-eminence in gastro-enterology and metabolism. Honorary members shall be entitled to attend all meetings and to take part in all proceedings but shall not be allowed to vote or to hold office.

## ARTICLE VI

### *Duties of Officers*

#### *President and Vice-President*

Section 1. The President shall preside at all meetings of the Association and shall be Chairman ex officio of the Governing Board. In his absence the first Vice-President shall preside, and in the absence of the President and the first Vice-President, the second Vice-President shall preside. The President and the Vice-President shall discharge the duties usually devolving upon such officers.

The President shall have the authority to appoint from the membership a delegate or delegates and alternates to co-operate in the activities of any recognized or approved medical or scientific society or association.

#### *Secretary*

Section 2. The Secretary shall attend all the meetings of the Association and of the Governing Board, of which latter he shall be ex officio clerk. He shall keep the minutes of all meetings and shall keep a list of all the members of the Association and at each annual meeting shall report the names of all those who have ceased to be members since the last meeting. He shall notify candidates of their election to membership and shall send notices of the annual meeting to all members of the Association.

#### *Treasurer*

Section 3. The Treasurer shall collect and receive all moneys and pay all debts on order of the President, Secretary, Recorder or two other members of the Governing Board. He shall keep accurate accounts, and shall render a statement at each meeting of the Governing Board and at the annual meeting.

His accounts shall be audited annually by a Committee appointed by the President at the annual meeting. He shall report to the Governing Board the names of all members whose dues are in arrears.

#### *Recorder*

Section 4. The Recorder shall secure all papers read at the annual meeting of the Association and see to their proper delivery to the Editor of our official journal, GASTROENTEROLOGY, and prepare proper and corrected notes of the discussions of the papers by members of the Association.

#### *Bylaws*

He shall conduct the Clinico-Pathologic Conference Section of the Journal, GASTROENTEROLOGY.

He shall be empowered to make various investigations and surveys of problems affecting the interests of the Association at the discretion or under the direction of the Governing Board, reporting his results to the Governing Board.

Any member essayist who does not submit his paper to the Recorder at the close of the meeting shall be denied the privilege of presenting a paper for three years.

### ARTICLE VII

#### *Duties of the Governing Board*

The Governing Board shall meet on call of the President of the Association or of any two members of the Governing Board as often as the interests of the Association may require and shall meet at least twice a year. Four members present shall constitute a quorum.

It shall be the duty of the Governing Board to supervise and manage all of the affairs of the Association, subject to the powers granted it in Article IV of the Constitution and subject to the provisions set forth in the Certificate of Incorporation.

It shall make all arrangements for the annual meetings, suggest subjects for discussion, consider and pass upon the eligibility of all candidates for membership and report on them at the next annual meeting of the Association.

Amendment: It shall have power to reject for publication such papers or discussions as it may deem unsuitable.

It shall have the power to invite any one not a member to attend and to read a paper at an annual meeting on any subject within the scope of the objects of the Association.

It shall have full power over and control of the Journal, GASTROENTEROLOGY; it shall appoint the Editor, Assistant Editor and Associate Editors; and it

shall represent the Association in its dealings with Williams & Wilkins, all subject to such action as the Association may take in executive session.

It shall receive the nomination of the Committee on the Julius Friedenwald Medal and shall recommend to the Association the recipient for the following year.

It shall have the power to investigate all charges of unprofessional or unbecoming conduct made against any member, and may make such investigations on its own initiative.

It shall make its own by-laws and rules of procedure but it shall keep accurate record of its doings and report same to the annual meeting of the Association.

## ARTICLE VIII

### *Duties of the Committee on Admissions*

It shall be the duty of the Committee on Admissions to investigate the merits of a candidate for membership and to report the results of its investigation to the Governing Board, in writing, as soon as possible.

It shall also be the duty of this Committee to prepare a list of candidates for advancement from Associate to Active membership and to submit same to the Governing Board for approval.

### *Bylaws*

To enable it to perform its duties hereunder this Committee shall study the active work in the science and practice of gastro-enterology and of metabolism in this country and Canada and to propose or have proposed for membership qualified candidates, and it shall file with the Secretary a complete report of its activities for the year.

## ARTICLE IX

### *Nomination of Officers*

The Officers and the Councilors, who, together constitute the Governing Board, shall be nominated by a committee of three members appointed by the President at each annual meeting, and this committee shall submit its report at the executive session of said meeting.

## ARTICLE X

### *Vacancies*

The Governing Board shall have the power to fill any vacancy occurring during the year among the Officers and Councilors of the Association. In the event of a vacancy in the offices of President and Vice-Presidents the Governing Board shall have the power to appoint a member temporarily to perform the duties of President.

## ARTICLE XI

### *Meetings*

Meeting of the Association shall be held annually at a time and place designated by the Governing Board.

## ARTICLE XII

### *Papers*

The Governing Board shall have the power to arrange the program for the annual meetings and to make rules and regulations with respect to papers and discussions at such meetings. It may, in its discretion, appoint a program committee consisting of the President, the Secretary and the Treasurer and delegate to it its powers under this article.

Any member desiring to offer to read a paper at an annual meeting shall forward to the Secretary the title of such paper, together with a printed or typewritten abstract thereof, at such times and under such conditions as the Governing Board may direct. Such abstract shall not exceed 300 words in length.

Unless otherwise arranged, all papers to be presented at an annual meeting shall not exceed a time limit of twelve minutes, and the presiding officer shall enforce the rule.

The Governing Board shall have the power to accept or reject any paper offered.

No paper shall be submitted and read before the Association which has already been published or read before another body. This regulation need not apply to guest speakers.

No paper shall be read by another member of the Association, i.e., if the title of a paper is listed on the program and the member assigned to read it finds it impossible to attend the meeting for any reason whatsoever, that paper shall be omitted from the program.

Members and guest speakers shall be required to leave their manuscripts with the Secretary or the Recorder before the close of the annual meeting.

The above rules and regulations shall remain in force unless and until altered by the Governing Board.

## ARTICLE XIII

### *Election of Members*

Section 1. All candidates for membership must be proposed in writing and all such proposals for membership, except Honorary membership, must be submitted to the Governing Board not later than December 10th of the year preceding the next annual meeting. The Secretary shall notify Senior and

Active members of all nominations for membership in the Association not less than one month previous to the date of the annual meeting.

Section 2. No proposal for membership shall be submitted to the annual meeting unless approved by the Governing Board. All elections of members shall be at the executive session of the annual meeting.

Section 3. Candidates for Honorary membership must be proposed in writing at any annual meeting by not less than six Active members, any or all of whom may be officers or members of the Governing Board, but the candidate shall not be voted upon until the next succeeding annual meeting. A unanimous vote of the Senior and Active members present at the annual meeting shall be necessary for the election of an Honorary member.

Section 4. Candidates for Active or Associate membership must be proposed in writing by two Senior or Active members, who are not members of the Governing Board, and must be accompanied by a letter from each proposer stating in detail his reasons for proposal of the candidate. The proposal must be accompanied by a list of the candidate's professional positions and published articles, a photograph, and such other information as the Governing Board may request.

Associate members shall be expected, during their probationary membership, to submit annually to the Secretary information regarding their activities, publications and changes in professional appointments. The failure of the Associate members to submit papers for presentation may be considered by the Governing Board as adequate basis for not advancing them to Active membership.

An affirmative vote of three-fourths of the Senior or Active members present at the executive session shall be necessary for the election of Active or Associate members.

Section 5. An associate member shall be eligible for election to Active membership at any time upon recommendation of the Governing Board.

If an Associate member is not advanced to Active membership within or at the end of five years his Associate membership shall automatically cease and he may not be proposed for re-election until after a lapse of two years and then only by permission of a majority of the Governing Board which shall not be granted if he was in arrears with his dues.

## ARTICLE XIV

### *Dues*

Section 1. The official year of the American Gastroenterological Association, Inc. is from January first to December thirty-first, inclusive.

Section 2. The entrance fee and dues shall be such as the Governing Board from time to time may determine.

Section 3. The annual dues shall include the subscription price of the official journal of the Association.

Section 4. Senior and Honorary members shall be exempt from the payment of dues.

Section 5. Wherever in other Articles of the Constitution or of the By-laws the term "arrears in dues" is used it shall be interpreted as one year as regards the receiving of the official journal and the Transactions, and two years as regards forfeiting membership in the Association.

Section 6. The Governing Board at its discretion may remit or reduce the dues of any member.

## ARTICLE XV

### *Transactions and Publications*

The official journal of the Association shall be *GASTROENTEROLOGY*, the Editorial Board of which shall be appointed by the Governing Board of the Association. The Editor or Assistant Editor shall report to the Governing Board at its meeting preceding the annual meeting of the Association, and more frequently if requested by the President, upon any and all matters relating to the Journal. The Editor shall serve as liaison officer between the Governing Board and Williams & Wilkins.

Active and Associate members not in arrears with their dues are entitled to receive the official journal of the Association, *GASTROENTEROLOGY*.

## ARTICLE XVI

The Committee on the Julius Friedenwald Medal shall consist of the President and First and Second Vice-Presidents of the Association, with the President acting as Chairman of the Committee, whose function shall be to recommend to the Governing Board the names for consideration as the recipient of the Julius Friedenwald Medal for the following year.

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\*Viggiano, F. A.: Dysmenorrhea in Industry—Treatment with a New Antispasmodic. Indust. Med. 15:632 (Nov.) 1946.

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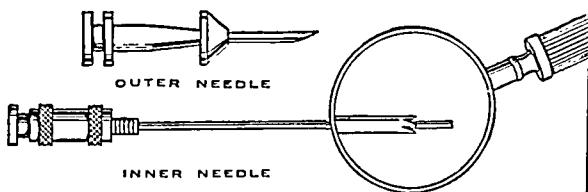
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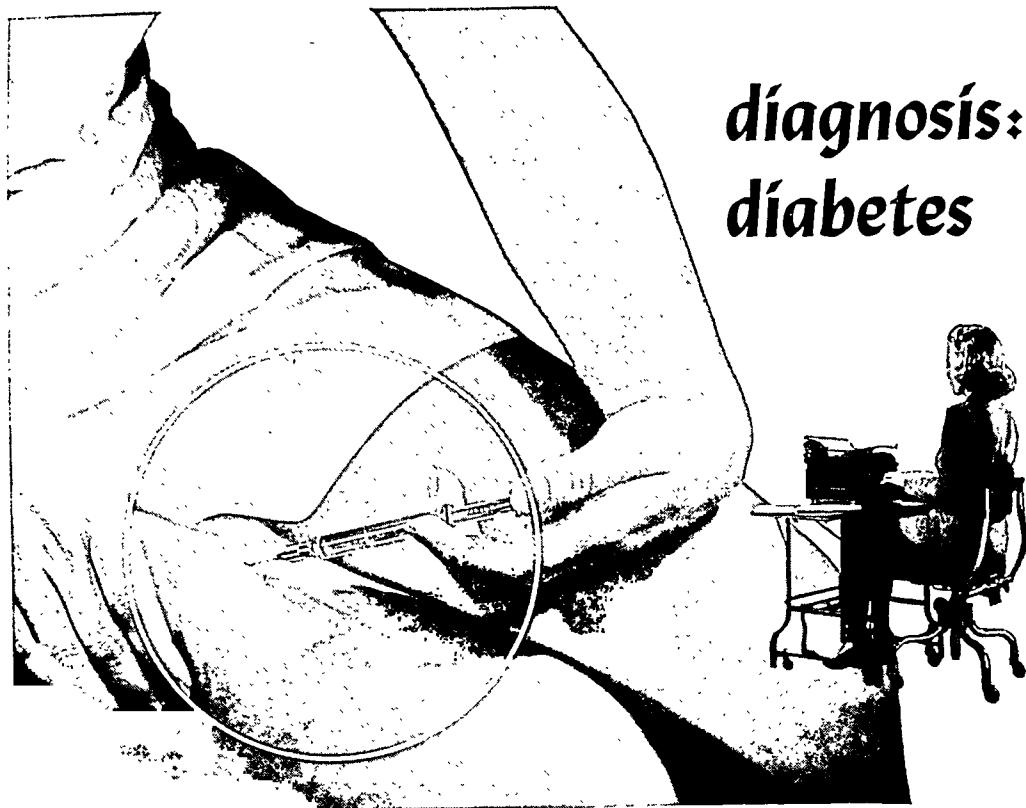
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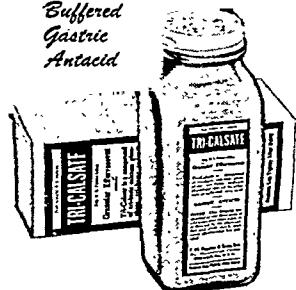


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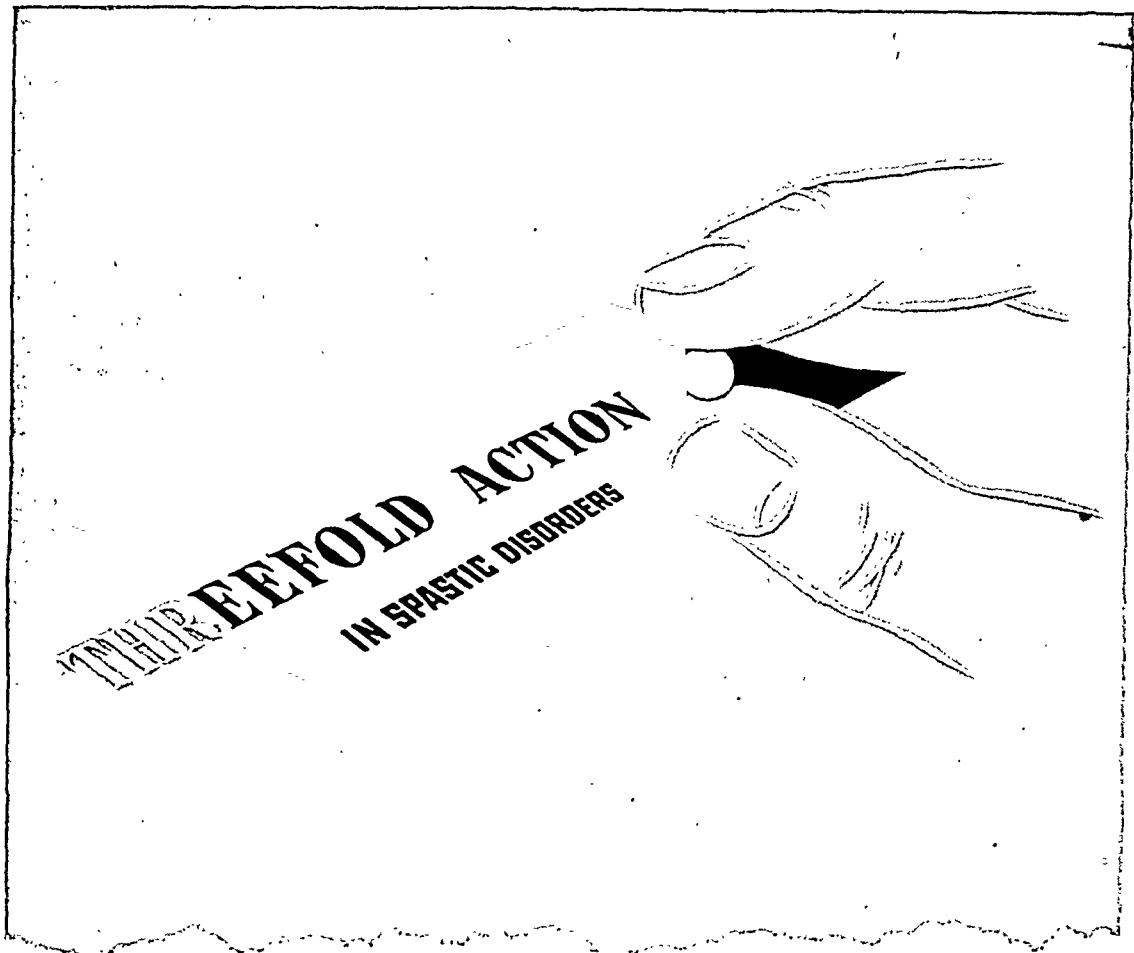
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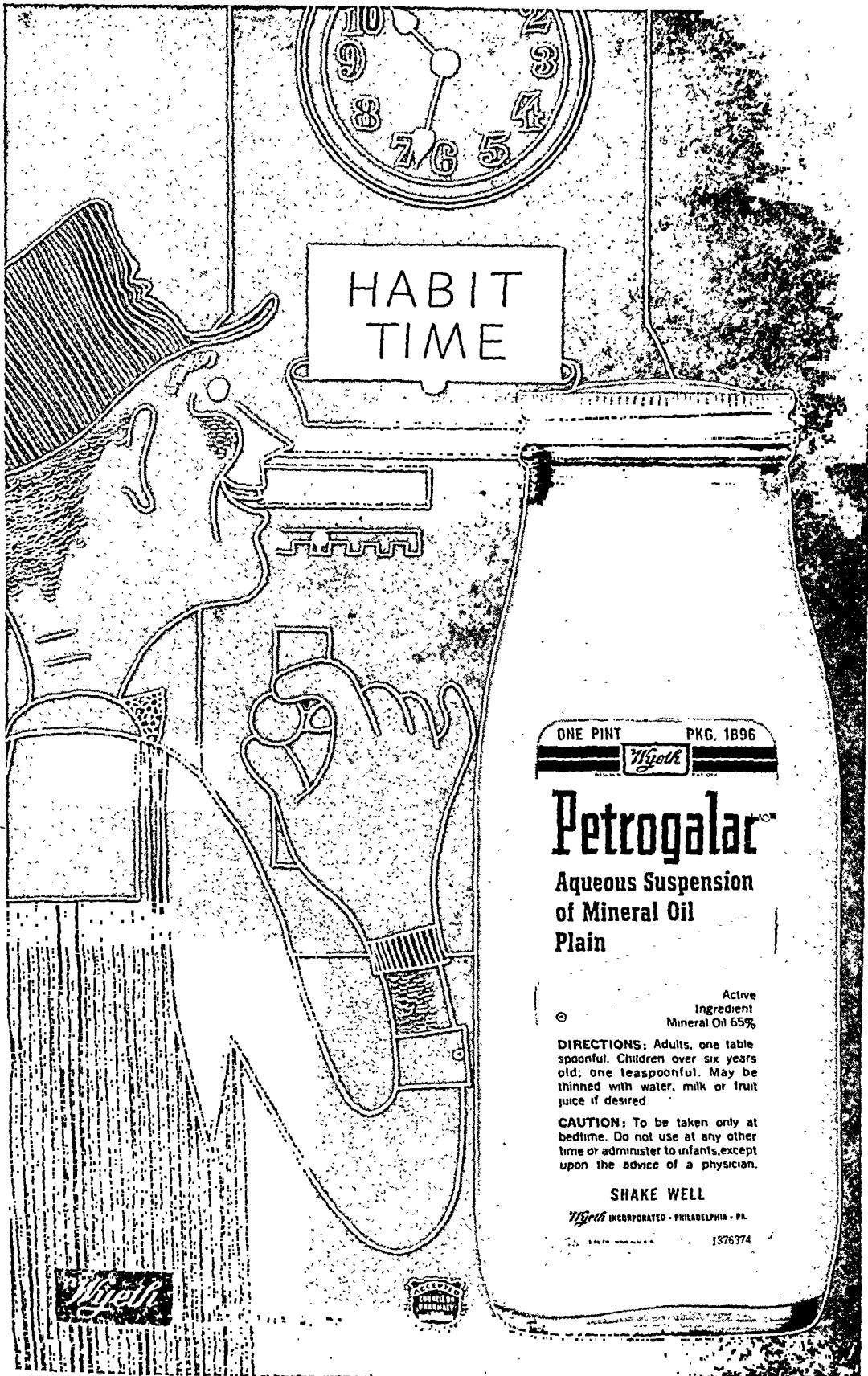
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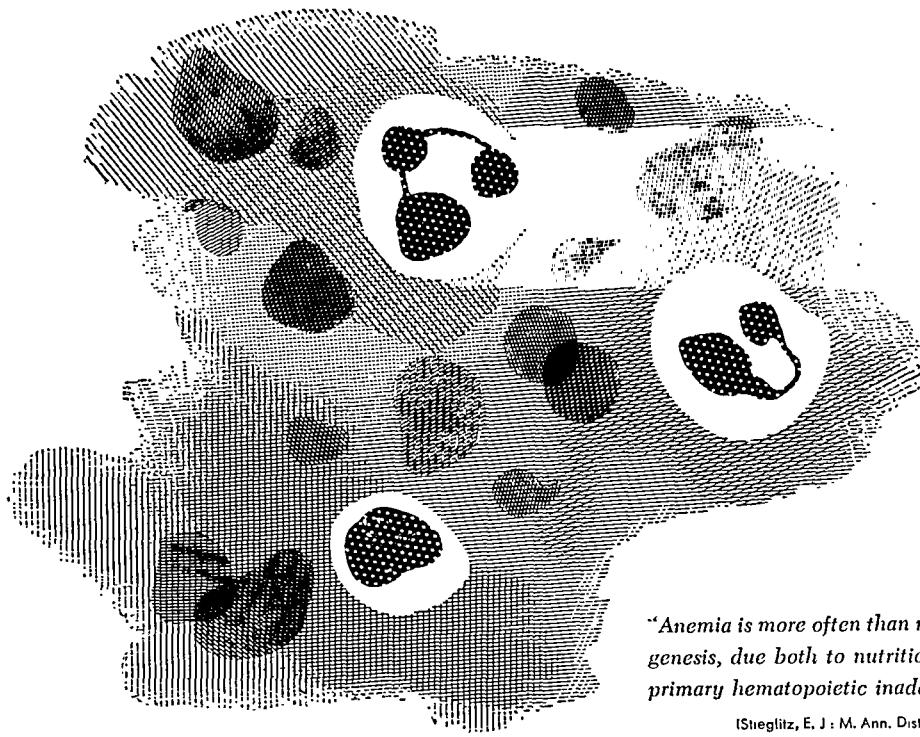
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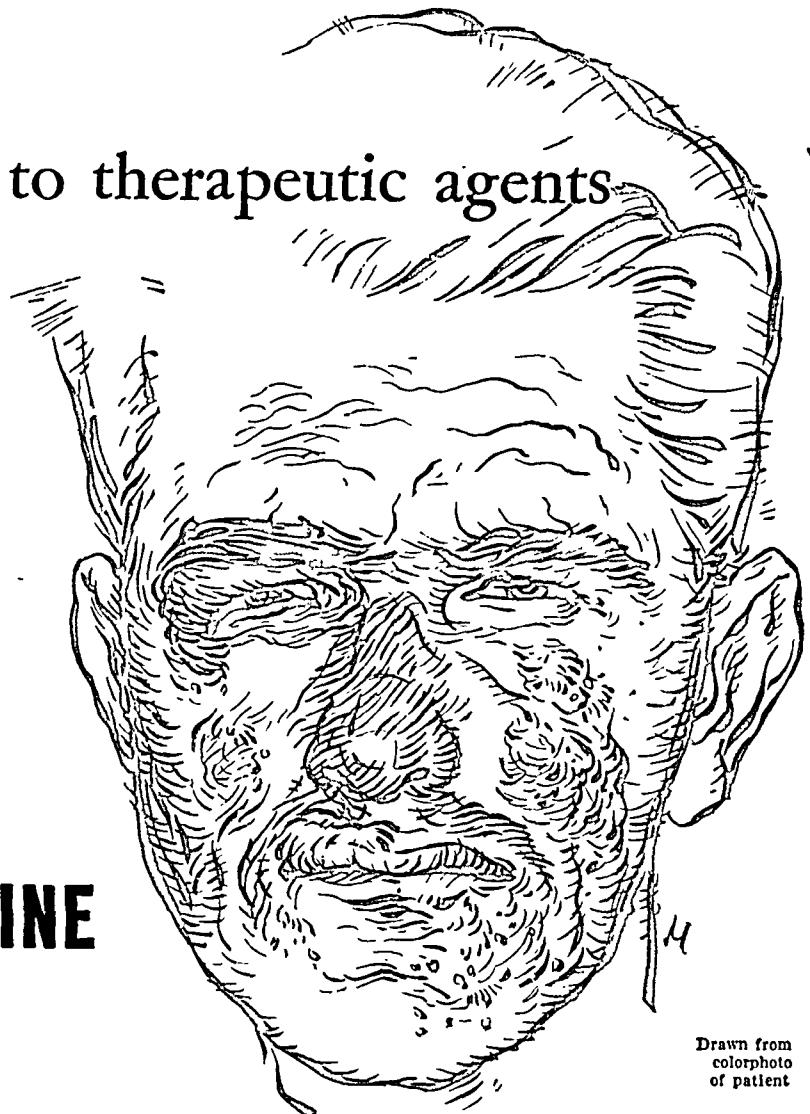
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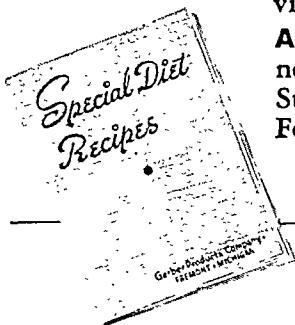
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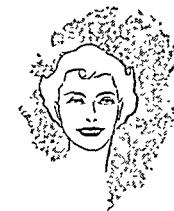
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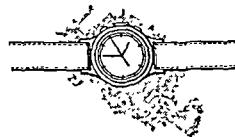
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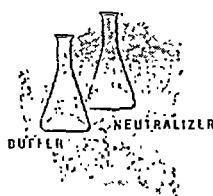
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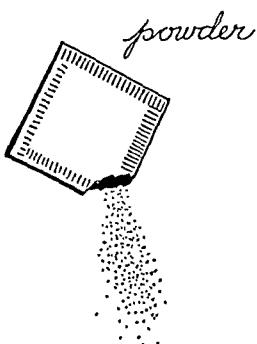
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- 1 Weiss, J.: Review of Gastroenterology, Nov., 1948
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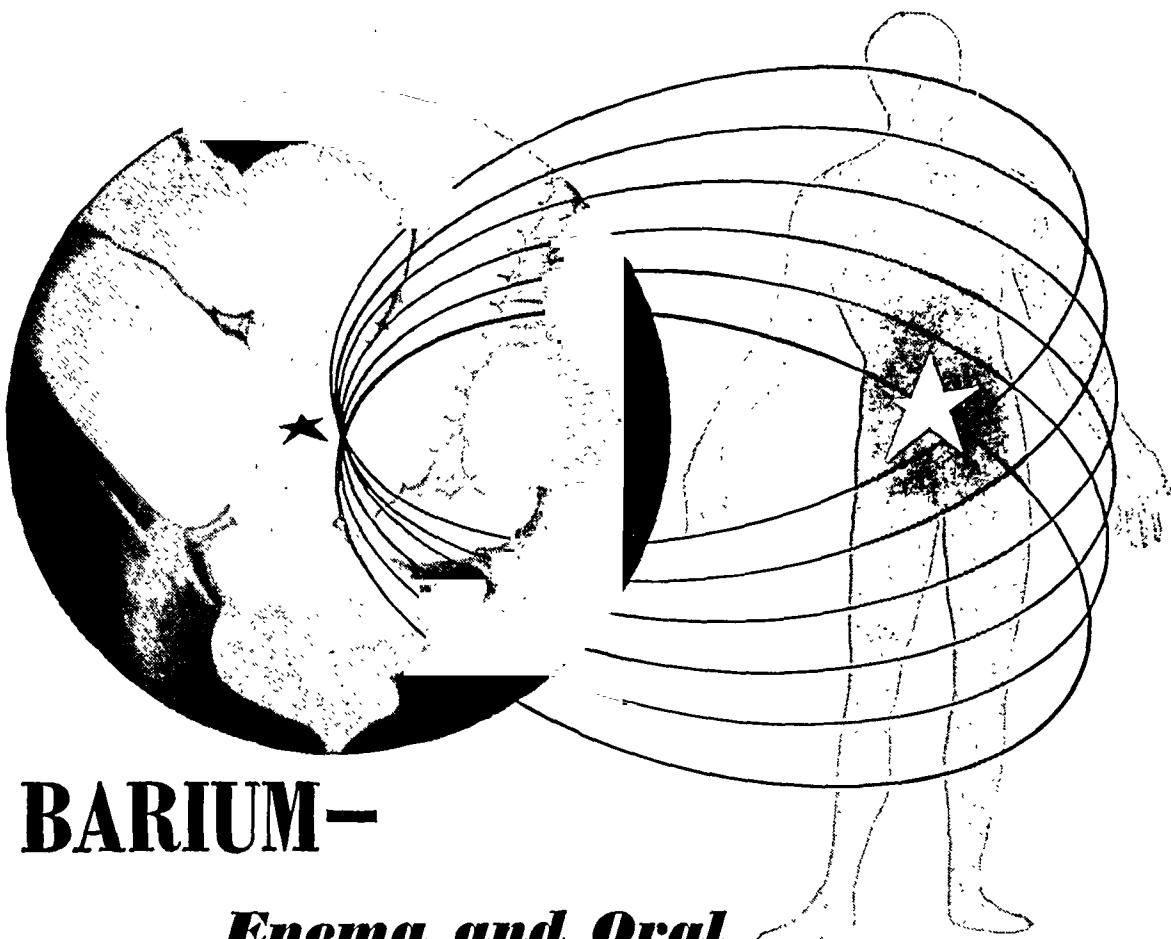
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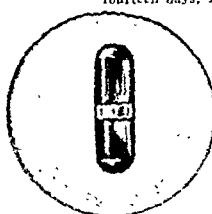
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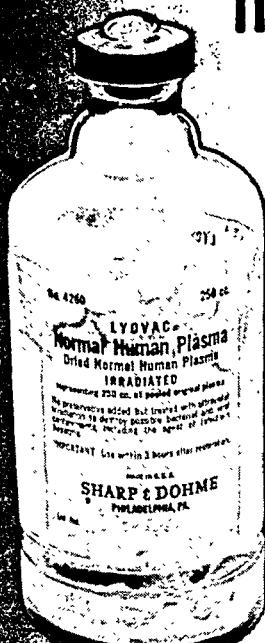
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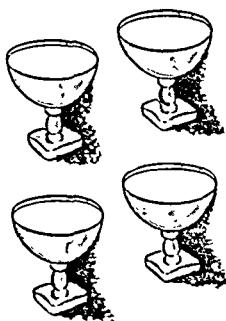
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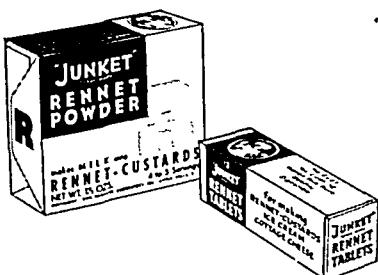
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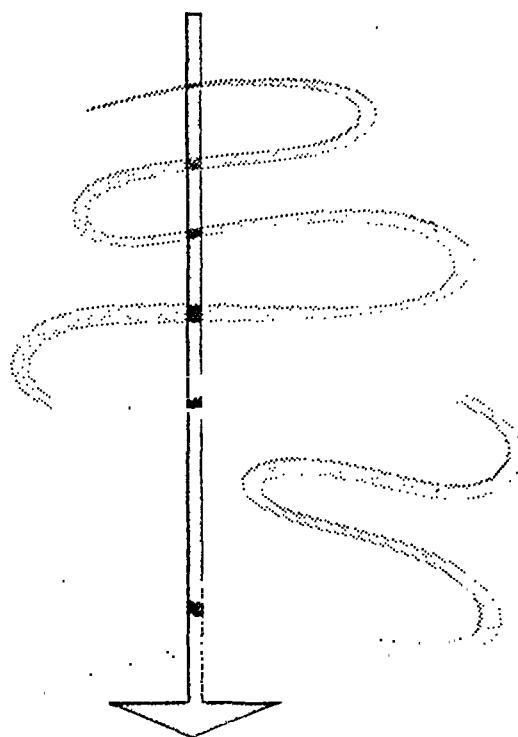
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# GASTROENTEROLOGY

*Official Journal of the American Gastroenterological Association*

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## RADIATION THERAPY IN PEPTIC ULCER: AN ANALYSIS OF RESULTS

WILLIAM E. RICKETTS, M.D., WALTER LINCOLN PALMER, M.D., JOSEPH B. KIRSNER, M.D., AND  
ANNA HAMANN, M.D.\*

*From the Frank Billings Medical Clinic, Departments of Medicine and Radiology, University of Chicago*

### INTRODUCTION

The purpose of this publication is to analyze the results of roentgen irradiation of the fundus and corpus of the stomach in more than 800 cases of peptic ulcer studied from 1936 to 1947. A previous paper<sup>1</sup> discussed the alterations in gastric secretion observed in the first hundred cases. Radiation therapy in peptic ulcer is based, first, upon the concept that acid gastric juice constitutes the sine qua non for chronic peptic ulcer and, second, upon the fact that roentgen irradiation depresses the secretory capacity of the stomach.

### HISTORICAL

Bruegel in 1917<sup>2</sup> was apparently the first to apply x-ray irradiation in the treatment of peptic ulcer. Numerous investigators have treated "hyperchlorhydria", gastric, duodenal and jejunal ulcer with variable doses of irradiation but without roentgenologic or gastroscopic control of the course of the ulcer and without adequate study of the effect on gastric secretion. The methods have differed considerably with respect to portals, quantity, intensity, total dosage duration and other factors, as pointed out by Desjardin<sup>13</sup>. Radiation of the pylorus and antrum, used in the treatment of polycythemia<sup>24-25</sup>, has not been observed to influence gastric secretion; tumoricidal doses in this area may produce necrosis and ulceration<sup>26-35</sup>.

Considerable differences in the effects of radiation are obtained by varying the amount of each single dose and the total dose. Englestad<sup>33-34</sup> found that in rabbits a single massive dose produced more ulcers and a higher mortality than the same total quantity given in separate doses. It has been shown experimentally that radiation effects are proportional to the amount of radiation<sup>32,33</sup>.

There is a striking uniformity in the effect on different elements of the stomach in various animal species despite the marked differences in the methods employed by various authors<sup>23, 33, 35, 27, 37, 43, 44</sup>. Moderate amounts

\* Presented before the American Gastroenterological Association in Atlantic City, May 1, 1948.

of radiation produce edema, degenerative changes of the epithelial cells, hyperemia, hemorrhage, and leukocytic infiltration; large doses produce necrosis with ulceration of the mucosa and of the muscular coats leading, at times, to perforation. The physical injury of irradiation affects all tissues in the irradiated areas, although certain cells are more damaged than others. The intestines are more sensitive than the stomach<sup>19-23</sup>. If radiation of moderate intensity is aimed at the acid secreting portions of the stomach through small portals, the danger of intestinal injury is minimal.

Since the original experimental studies of Regaud, Nogier, and Lacassagne in 1912<sup>45</sup>, the effect of irradiation on gastric secretion has been unclear although, except for a few dissenters, nearly all investigators agree that a decrease occurs, the effect varying with the amount of radiation<sup>1, 2, 15, 17, 29, 37, 42, 46, 59</sup>. Palmer and Templeton<sup>1</sup> found transitory reduction in secretion in all cases; in 35 of the 88 patients studied histamine achlorhydria occurred. Further study<sup>60</sup> of the nocturnal fasting secretion disclosed a reduction of volume averaging 47.4 per cent, with complete anacidity in 13 of the 15 individuals receiving a depth dose of 1600 r.

Several observers,<sup>29, 15, 52</sup>, have found a marked decrease in pepsin as well as hydrochloric acid; however, Miescher<sup>15</sup> found no strict parallelism.

#### METHODS

##### *Technique of Irradiation*

As shown in Table 1, four different techniques have been used in our work from 1936 to 1948 although certain factors remained the same in all. These are the quality of the radiation of H.V.L. 1.5 mm. cu produced by 200 PKV and 1 mm. cu plus 1 mm. Al. filtration, and an intensity of the radiation of approximately 33 r in air per minute obtained with 20 M.A. and 50 Cm. F.S.D. In all techniques two portals opposite to each other were irradiated, one located in the left hypochondrium and the other in the left costo-lumbar region (Fig. 1). As the stomach lies closer to the anterior wall than to the posterior, the depth dose in the gastric fundus and corpus of the stomach was estimated in a plane of the patient which lies  $\frac{1}{3}$  of the anterior posterior diameter from the front portal and  $\frac{2}{3}$  of the same diameter from the back portal. The fundus and corpus of the stomach may deviate from this plane but the variation in the depth dose from  $\frac{1}{4}$  of the diameter from the front to  $\frac{1}{4}$  from the back is, with our factors, only in the order of 10 per cent; therefore, the actual dose given to the upper portion of the stomach is very close to the estimated dose.

In technique A the size of the portal was 15 x 15 cm. or occasionally 20 x 20 cm. Five treatments were given to the anterior portal and five to the posterior. The treatments were given daily and the portals treated alternately.

The total depth dose in the gastric fundus and corpus varied with the size of the patient from 1600 to 2500 r in 12 days. The great variation in dosage

TABLE 1  
*Techniques of irradiation*

TECHNIQUES	NO. TREATMENTS PER PORTAL*	DURATION RADIATION	PORTALS IN CM.	DEPTH DOSE TO GASTRIC FUNDUS IN r
A	5-6	12-14	15 x 15 (rarely) 20 x 20	1600-2500 r
B†	5-8	11-14	13 x 13	1600 r
C	5	11-12	13 x 13	1100-1500 r
D	3	6-7	13 x 13	666-1000 r

\* In obese patients both portals were treated on the same day.

† In Technique B the depth dose was fixed, the surface dose varying with the diameter of the patient. In Techniques A, C, and D the surface dose was fixed and the depth dose in the fundus and corpus of the stomach varied.

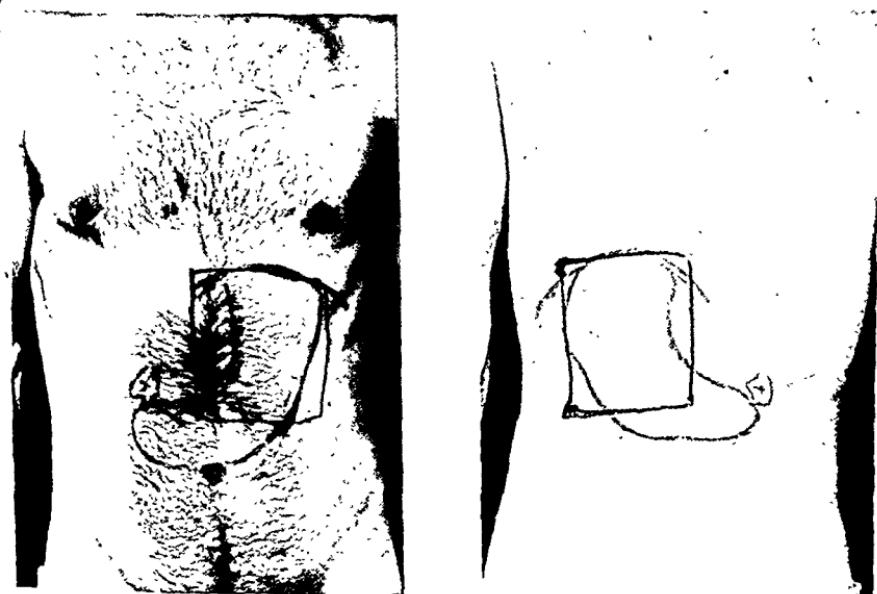


FIG. 1. APPROXIMATE PORTALS USED IN ANTERIOR AND POSTERIOR RADIATION OF THE FUNDUS AND CORPUS OF THE STOMACH

resulted from the use of a constant air dosage without regard for the size of the portal or the size of the patient.

Technique B consisted in 5-8 single treatments per portal, 13 x 13 cm. square, during 11 to 14 days. The depth dose was 1600 r, made as uniform as possible

according to the size of the patient by varying the number of single treatments. In order not to prolong the total treatment for more than 12 days, the obese patients received treatment to both portals on the same day.

In technique C the size of the portal was 13 x 13 cm. and ten treatments were given, five to each portal. The total depth dose varied from 1000 to 1500 r in 11 to 12 days.

In technique D the total number of treatments was six, three to each portal. The size of each portal was 13 x 13 cm., or occasionally 15 x 15 cm. The depth dose in the gastric fundus and corpus varied from 600 to 1000 r in 6-7 days.

In retrospect, because of the variation in the position of the stomach, it would have been advisable to determine fluoroscopically the exact position of the gastric fundus and corpus prior to the irradiation, thus avoiding unnecessary radiation of other tissues and insuring radiation of the desired areas. However, this precaution was not taken in the great majority of our cases, the radiation being directed at a location found to be the usual position of the stomach. This error may account for some of the failures; fluoroscopic control is now routine.

#### DETERMINATION OF GASTRIC SECRETION

Gastric secretion was measured in terms of the *maximum* free acidity, expressed as clinical units of titratable acid using Topfer's solution, obtained in response to the standard histamine test using 0.01 mg. of histamine hydrochloride, subcutaneously, per kilogram of body weight. Specimens were collected every ten minutes for 90 minutes. The term "achlorhydria" indicates that no free acid was found after histamine.

#### RESULTS

##### *Effect on Gastric Secretion*

It was possible to follow fairly satisfactorily the course of 423 patients. The over-all effects are shown in Table 2. There was a direct correlation between the decrease of the hydrochloric acid and the total amount of radiation delivered.

In 300 patients with duodenal ulcer not receiving radiation therapy, but under similar conditions of treatment, no significant decrease in histamine secretion was observed. The variations within each group were very great as will be shown later. Similar doses of irradiation produced somewhat different results in patients with gastric, duodenal and jejunal ulcer, due, presumably, to the different secretory rates; hence the results will be analyzed separately.

## GASTRIC ULCER

Radiation proved to be a potent depressor of secretion in 47 cases treated (Table 3). In 32 cases, there was anacidity; in an additional 10 the free acidity dropped at least 50 per cent from the original value; and in only 5 was the maximum decrease less than 50 per cent. Radiation with technique A

TABLE 2  
*Depression of gastric acidity—over-all results*  
(423 Cases)

REDUCTION OF ACID	TYPE OF RADIATION							
	D 666-1000 r		C 1100-1500 r		B 1600 r		A 1600-2500 r	
	No. cases	Per cent	No. cases	Per cent	No. cases	Per cent	No. cases	Per cent
Achlorhydria (Histamine).....	2	9	56	25	56	47	44	76
50 per cent or more.....	5	23	77	34	36	30	6	11
Less than 50 per cent.....	15	68	90	41	28	23	8	13
Total.....	22	100	223	100	120	100	58	100

TABLE 3  
*Effect on histamine secretion in gastric ulcer*

MAXIMUM DEPRESSION OF ACIDITY	NO. CASES	PER CENT	TYPES OF RADIATION					
			A		B		C	
			No. cases	Per cent	No. cases	Per cent	No. cases	Per cent
Achlorhydria.....	32	68	10	91	11	92	11	48
Reduced 50 per cent or more but without achlorhydria.....	10	21	1	9	0	9	4	36
Less than 50 per cent reduction.....	5	11		0	1	8		16
Total.....	47	100	11	100	12	100	24	100

was effective in 100 per cent of the patients, technique B in 92 per cent and technique C in 84 per cent. No patients with gastric ulcer were treated with technique D, for entirely fortuitous reasons.

The depression usually occurred very promptly, as shown in Table 4. In nearly two-thirds of the patients anacidity occurred within less than a month. This immediate effect is coincident with inflammatory changes in the mucosa, evident gastroscopically and histologically<sup>62</sup>. These changes are, in general, transitory. An uncommon late reaction with achlorhydria is coincident with atrophy of the mucosa. Histologically, the mucosa presents a striking bizarre

appearance with various combinations of atrophy, proliferation, metaplasia and fibrosis<sup>36</sup>.

The duration of the achlorhydria in 32 cases, as shown in Table 5, was quite variable, the shortest being a few days and the longest eight years up to the

TABLE 4  
*Interval between radiation and the occurrence of achlorhydria in gastric ulcer*

LENGTH OF TIME	NO. CASES	TYPE OF RADIATION		
		A	B	C
Less than 1 month.....	20	5	7	8
1-3 months.....	8	4	3	1
3-6 months.....	2		1	1
6 months-1 year.....	1			1
More than 1 year.....	1	1*		
Total.....	32	10	11	11

\* Nearly 3 years.

TABLE 5  
*Duration of achlorhydria in gastric ulcer*

LENGTH OF TIME	NO. CASES	A	B	C
Less than 30 days.....	9	3	2	4
30-90 days.....	6	2	2(1)	2(2)
3-6 months.....	6	1	3(1)	2
6 months-1 year.....	1		1	
1-2 years.....	2	1	1	
2-4 years.....	3	1	1	1(1)
4-6 years.....	1			1(1)
6-10 years.....	2	1(1)		1(1)
Unknown.....	2	1	1	
Total.....	32	10	11	11

Numbers in parentheses indicate the minimum length of anacidity, as in these cases no further follow-up could be made.

present. In this instance, the mucosa changes as seen by gastroscopy seem permanent.

#### DUODENAL ULCER

While more than 700 cases of duodenal ulcer have been treated with roentgen radiation in the last 12 years, satisfactory studies are available in only 352, as shown in Table 6. The periods of observation have been from 1 to 11 years. The effects on secretion varied in general with the total amount of radiation

delivered, as is illustrated in Table 6. Technique A produced achlorhydria in 50 per cent, reduction of the free acidity by at least a half in an additional 33 per cent, and no significant reduction (less than half) in 17 per cent, whereas technique D produced achlorhydria in 9 per cent, significant decrease of the

TABLE 6  
*Effect on histamine secretion in duodenal ulcer*

MAXIMUM DEPRESSION OF ACIDITY	NO. CASES	PER CENT	TYPES OF RADIATION THERAPY							
			A		B		C		D	
			No. cases	Per cent	No. cases	Per cent	No. cases	Per cent	No. cases	Per cent
Achlorhydria.....	108	29	23	50	43	40	40	22	2	9
Reduced 50 per cent or more but without achlorhydria.....	108	32	15	33	37	34	53	31	3	14
Less than 50 per cent reduction .....	136	39	8	17	27	26	84	47	17	77
Total.....	352	100	46	100	107	100	177	100	22	100

TABLE 7  
*Duration of achlorhydria in duodenal ulcer*

DURATION OF ACHLORHYDRIA	NO. CASES	TYPE OF RADIATION			
		A	B	C	D
Less than 1 month.....	46	10	16(5)	19(7)	1
1-3 months.....	33	6(1)	16(7)	10(3)	1
3-6 months.....	13	3	4(1)	6	
6 months-1 year.....	7	3(1)	3	1	
1-2 years.....	5	1	2	2(2)	
2-4 years.....	2		1	1(1)	
4-6 years.....	1		1(1)		
6-10 years.....	1			1(1)	
Total.....	108	23	43	40	2

Numbers in parentheses indicate the minimum length of anacidity, as in these cases no further follow-up could be made.

free acid in an additional 14 per cent, and no significant reduction in 77 per cent.

Achlorhydria occurred in 108 cases of the 362 cases studied, an overall incidence of 29 per cent. The duration of the achlorhydria in two-thirds of these was less than 3 months. The duration was as unpredictable as it was variable; in one patient, it has lasted for 8 years.

## JEJUNAL ULCER

The results in 15 patients with jejunal ulcer were as follows: In one receiving technique A, achlorhydria lasted 2 months; in two cases receiving technique B, achlorhydria lasted for 2 weeks and nearly 3 months respectively; of 12 receiving technique C, five developed achlorhydria lasting less than three months, five had a significant and two an insignificant reduction in acidity. None developed achlorhydria lasting for more than 3 months; in 5 patients the post-radiation levels of acidity remained considerably lower than the pre-radiation levels.

*Effect on the Ulcer*

The effects of radiation therapy on peptic ulcer are analyzed with respect to (a) healing and (b) recurrence. The over-all results are shown in Table 8.

TABLE 8  
*Healing of ulcer after irradiation*  
(Overall results)

RADIATION TECHNIQUE	NO. PATIENTS TREATED	HEALED	PER CENT
A (1600-2500 r)	49	46	93.8
B (1600 r)	101	89	88.1
C (1100-1500 r)	160	146	91.2
D (666-1000 r)	24	17	70.0
Total.....	334	298	89.2

It will be noted that the percentage of healing increased from 70 per cent in Group D, receiving the smallest amount of radiation, to 93.8 per cent in Group A, receiving the largest dosage. It should be pointed out that in none of these groups is radiation therapy considered solely responsible for the healing. We are aware of the frequency of spontaneous healing, of the role of psychotherapy, and of the importance of the dietary and antacid management of the Sippy type which these patients all received. The results do suggest, however, that the difference between 70 per cent healing in Group D and 93.8 per cent in Group A is attributable to the radiation.

## GASTRIC ULCER

In 50 patients with gastric ulcer radiation was included in the program of management, and the course of the lesion observed for a sufficient period of time to permit evaluation of the procedure, i.e., one month or longer. Healing occurred in 90 per cent, as shown in Table 9.

This result may be contrasted with a 60 per cent incidence of healing in 114

patients with gastric ulcer treated by medical management alone, as shown in Table 10.

There was no correlation between the age of the patient or the duration of symptoms and the subsequent healing (Tables 11 and 12).

TABLE 9  
*Healing of gastric ulcer (50 cases)*

RADIATION TECHNIQUE	NO. PATIENTS TREATED	COMPLETE HEALING	PER CENT
A (1600-2500 r)	15	14	93
B (1600 r)	13	11	84
C (1100-1500 r)	22	20	90
Total.....	50	45	90

TABLE 10  
*Gastric ulcer*  
Comparison between cases treated with and without radiation therapy

	MEDICAL TREATMENT ALONE		MEDICAL TREATMENT PLUS RADIATION THERAPY	
	No. cases	Per cent	No. cases	Per cent
Healing.....	69	60	45	90
No Healing.....	45	40	5	10
Total.....	114	100	50	100

TABLE 11  
*Age of patient and results of treatment in gastric ulcer*

AGE	CASES HEALED	CASES UNHEALED
31-40	7	1
41-50	17	1
51-60	13	3
61-70	7	
More than 70	1	
Total.....	45	5

In 71 per cent of the cases healing of the ulcer occurred in less than 90 days, as shown in Table 13.

#### RECURRENTS

The marked tendency of gastric ulcer to recur is illustrated by the fact that recurrence was observed in one-third of the patients followed for longer than a

TABLE 12  
*Duration of disease and results of treatment in gastric ulcer*

LENGTH OF DISEASE	CASES HEALED	CASES UNHEALED
Less than 6 months.....	12	2
6 months-1 year.....	3	1
1-2 years.....	2	1
2-4 years.....	6	0
4-6 years.....	7	0
6-10 years.....	6	0
10-15 years.....	3	0
More than 15 years.....	6	1
Total.....	45	5

TABLE 13  
*Interval between completion of radiation therapy and complete healing\* of the gastric ulcer*

INTERVAL	NO. CASES	TYPE OF RADIATION THERAPY		
		A	B	C
Less than 30 days.....	10	3	2	5
30-45 days.....	8	3	2	3
45-90 days.....	14	6		8
90 days-6 mos.....	10	1	6	3
6 mos.-1 year.....	11			1
1 year-2 years.....	1	1		
Undetermined.....	1		1	
Total.....	45	14	11	20

\*As denoted by roentgen and gastroscopic examinations.

TABLE 14  
*Recurrence of gastric ulcer (1-10 years)*

TECHNIQUE OF RADIATION	NO. OF CASES FOLLOWED	RECURRENCE	
		No. cases	Per cent
A (1600-2500 r)	11	6	54
B (1600 r)	9	2	22
C (1100-1500 r)	16	4	25
Total.....	36	12	33

year and as long as ten years (Table 14). This incidence contrasts with 80 per cent recurrence noted in gastric ulcers treated medically without radiation.

There was no correlation between the age of the patient and the recurrence. (Table 16).

The length of time from the complete healing of the ulcer to recurrence as evidenced by gastroscopy and roentgen examinations in 12 patients is shown in

TABLE 15  
*Incidence of recurrence in gastric ulcer with and without radiation therapy*

COURSE	MEDICAL TREATMENT ALONE		RADIATION THERAPY	
	No. cases	Per cent	No. cases	Per cent
Recurrence.....	23	70	12	33
No Recurrence.....	10	30	24	67
Total.....	33	100	36	100

TABLE 16  
*Lack of correlation between recurrence and age of patient  
(Gastric ulcer)*

AGE	NO. CASES	
31-40		3
41-50		4
51-60		4
61-70		1
More than 70		
Total.....		12

TABLE 17  
*Interval between healing and recurrence  
(Gastric ulcer)*

LENGTH OF TIME	NO. CASES	TYPE OF RADIATION		
		A	B	C
Less than 2 mos.....	1	1		
2-6 months.....	4	2		2
6 mos.-1 year.....	1	1		
1 year-2 years.....	6	1	1	4
2-4 years.....				
Longer than 4 years.....				
Total.....	12	4	1	6

Table 17. It will be seen that the recurrences all appeared within two years after the radiation.

Patients with achlorhydria of 3 months or longer constitute a striking group, for in only 3 of 15 such patients (20 per cent) have recurrences been observed

as yet. Of 15 patients with achlorhydria longer than 3 months, 6 have continued to manifest achlorhydria; the longest period is now over 8 years; 3 patients have continued with secretory levels at least 50 per cent below the prerdiation values; in 6 the free acid has returned to its previous level. In no instance has the ulcer recurred during the period of achlorhydria.

#### DUODENAL ULCER

The results of treatment could be followed in 272 cases. As shown in Table 18, after techniques A, B and C the incidence of healing varied from 88 to 95

TABLE 18  
*Healing of duodenal ulcer*

TECHNIQUE OF RADIATION	NO. PATIENTS TREATED	HEALED	PER CENT
A (1600-2500 r)	37	35	95
B (1600 r)	88	78	88
C (1100-1500 r)	123	112	91
D (666-1000 r)	24	17	70
Total.....	272	242	89

TABLE 19  
*Interval between radiation and roentgen disappearance of duodenal ulcer crater*

LENGTH OF TIME	NO. CASES	TYPES OF RADIATION THERAPY			
		A	B	C	D
Less than 45 days.....	100	11	24	60	5
45-90 days.....	61	9	22	26	4
3-6 months.....	34	3	16	12	3
6 months-1 year.....	8	1	7		
1-2 years.....					
Unknown.....	39	11	9	14	5
Total.....	242	35	78	112	17

per cent, whereas in technique D, healing occurred in 70 per cent. The ulcers which did not heal invariably occurred in patients in whom the free acidity was not significantly reduced.

The length of time required for complete healing after radiation is shown in Table 19. It will be seen that in four-fifths of the cases the ulcer healed in less than 3 months. As with gastric ulcer, in duodenal and also in jejunal ulcers, there was no correlation between the duration of the disease or the age of the patient and the healing of the ulcer. There was a direct correlation with the abolishment of the free hydrochloric acid.

Healing of the ulcer was evidenced by disappearance of the crater seen roentgenologically, but not by the disappearance of the deformity, except in very few instances. Patients with achlorhydria lasting for several years continued to have deformity of the duodenum.

TABLE 20  
*Recurrence of duodenal ulcer (1-10 years)*

TECHNIQUE OF RADIATION	NO. PATIENTS FOLLOWED	RECURRENCE	
		No. patients	Per cent
A (1600-2500 r)	32	11	34
B (1600 r)	55	16	30
C (1100-1500 r)	54	13	24
D (666-1000 r)	15	10	66
Total.....	156	50	32

TABLE 21  
*Interval between healing and recurrence (duodenal ulcer)*

LENGTH OF TIME	NO. CASES	TYPES OF RADIATION THERAPY			
		A	B	C	D
Less than 1 month.....					
1-3 months.....					
3-6 months.....	4		2	2	
7 mos. to 1 year.....	10	1	6	2	1
1-2 years.....	17	3	7	3	4
2-4 years.....	9	3	1	4	1
4-6 years.....	9	4		2	3
6-10 years.....	1				1
Total.....	50	11	16	13	10

#### RECURRENCES

Of 156 cases of duodenal ulcer followed for longer than one year and as long as 10 years, recurrence took place in two-thirds of those receiving minimal radiation and in approximately one-third of those receiving the larger amounts (Table 20). The time from complete healing to recurrence of the ulcer is expressed in Table 21. Recurrences developed in from 6 months to 2 years after healing. The recurrence of the ulcer in some cases immediately followed the reappearance of acid in the gastric secretion. In other cases recurrence did not take place despite the reappearance of acid. In 29 cases in which radiation resulted in achlorhydria for longer than 3 months, recurrence occurred in only 4, an incidence of 14 per cent. Return to the previous secretory levels was observed in approximately two-thirds of the patients.

## JEJUNAL ULCER

Irradiation was given in twenty cases of jejunal ulcer occurring after gastro-enterostomy for duodenal ulcer; Techniques A, B and C were utilized. Healing occurred in 19 of the 20, an incidence of 95 per cent (Table 22). The one unhealed case had no depression of the gastric secretion.

Recurrence of the ulcer was observed in nine of seventeen patients followed for longer than one year (Table 23).

TABLE 22  
*Healing of jejunal ulcer*

RADIATION TECHNIQUE	NO. PATIENTS TREATED	HEALED	PER CENT
A (1600-2500 r)	1	1	100
B (1100-1500 r)	2	2	100
C (666-1000 r)	17	16	91
Total.....	20	19	95

TABLE 23  
*Recurrence of jejunal ulcer after irradiation*

TECHNIQUE OF IRRADIATION	NO. CASES	RECURRENCE	PER CENT
A (1600-2500 r)	1	0	0
B (1600 r)	2	1	50
C (1100-1500 r)	14	8	57
Total.....	17	9	53

## DISCUSSION

The healing of ulcer as a result of decreased peptic activity in dogs following radiation was beautifully shown experimentally by Miescher in 1923<sup>37</sup>. At the opening of the gastric fistula in a Pavlov pouch dog a traumatic ulcer in the skin had grown to considerable size as a result of the digestive action of the gastric juice. After the administration of x-ray there was complete healing in about two months; after the return of the acidity to normal the ulcer formed anew. With the next application of x-rays it again disappeared. The author observed that the healing factor was not in direct relation to the roentgen ray effect on the ulcer, but rather to the lowering of the acidity of the gastric juice. Case and Boldyreff<sup>38</sup> reported a similar experience with a rebellious ulcer, 2.5 cm. in diameter, around the fistula of the isolated stomach of a dog, which persisted for ten months despite treatment, but healed rapidly within three weeks after roentgen irradiation.

The reported contradictory effects of radiation on gastric secretion and in the treatment of peptic ulcer are probably due to the different methods used and the variable amounts of radiation delivered. Paradoxically, radiation may produce ulcers or bring about the healing of ulcers. Radiation of the fundus and body of the stomach may result in healing by way of the decreased secretion and consequent decrease in peptic activity; on the other hand, massive radiation, particularly of the antrum, as in tumor therapy, may cause tissue necrosis and ulceration. The problem to be solved is whether there is a technique and a dosage adequate to depress gastric secretion sufficiently in terms of amount and duration to permit healing of peptic ulcer and to protect against recurrence, without seriously injuring the skin, the stomach or intervening organs.

The evidence indicates a direct correlation between depression of gastric secretion and healing of the ulcer; there is no correlation between the age or sex of the patient or the duration of symptoms and healing. In each of 44 patients with achlorhydria persisting for three months or longer the ulcer healed completely.

When irradiation is delivered to the acid secreting portions of the mucosa, all phases of secretion, chemical, cephalic, and intestinal, are depressed as a result of direct cellular injury. Ivy and his co-workers<sup>40</sup> radiated half of a Pavlov pouch in several dogs; the radiated portions secreted little or nothing after various types of stimulation. Portis and Ahrens<sup>50</sup> confirmed this observation. Radiation delivered to portions of the body other than the stomach does not affect gastric secretion<sup>25</sup>.

Marked individual variations occur in patients receiving the same amount of radiation, corroborating the view that the result depends not merely upon the amount of radiation given, but also upon the variable and unpredictable tissue susceptibility. Statistically, however, the effect varies in direct proportion to the amount given, all other factors being equal.

The doses used in the present studies are considerably less than those which may produce necrotic lesions in the stomach. Such lesions may be produced by massive irradiation of hollow viscera, regardless of the presence or absence of hydrochloric acid, as is evidenced by the formation of bowel and rectal ulcerations after the radiation of pelvic organs.

It is interesting to note that Brick<sup>16</sup>, after delivering huge doses of 5000 to 6000 r to the gastric antrum in tumor therapy, observed no change in the gastric secretion. This observation might be used as an argument against the existence of a pyloric organ elaborating a hormone which stimulates the acid secreting glands in the upper half of the stomach.

In this series there was a correlation between the lowering of the secretion and the amount of radiation. A dose of 1600 r to 2500 r significantly reduced

the acid (more than 50 per cent) in all patients with gastric ulcer and in 83 per cent of those with duodenal ulcer; 1600 r significantly reduced the acid in 92 per cent of those with gastric ulcer and 84 per cent of those with duodenal ulcer; a dose of 1100 to 1600 r decreased the acidity in 82 per cent of the patients with gastric ulcer and 53 per cent of those with duodenal ulcer; a dose of 600 to 900 r (type D) reduced the acidity in only 23 per cent of the patients with duodenal ulcer.

The decrease in secretion usually developed in less than 30 days after the completion of radiation. There were a few instances, however, in which the decrease was slow and progressive; in one, achlorhydria developed 5 months after the completion of the course and lasted for nearly two months.

Acute changes in the mucosa as the immediate effect of radiation may be seen both gastroscopically and histologically<sup>61</sup>. Many months and years later permanent achlorhydria may develop, with gastroscopic evidence of atrophy. This is probably a sequel of the previous radiation, as reported in another paper<sup>62</sup>. In such instances, irradiation may permanently abolish the hydrochloric acid. The patients who developed achlorhydria for several years were clinically well in spite of the atrophy seen gastroscopically<sup>61</sup>.

The effects of radiation therapy have been regarded as transitory by most investigators. In one-third of the present group of cases of gastric ulcer the acidity never returned to its previous level and, in some, permanent achlorhydria developed. The duration of the achlorhydria varied from a few days to eight years at the present time.

In no instance was ulcer pain present during the phase of achlorhydria, regardless of whether or not the ulcer had healed; indeed, the pain almost always disappeared on ulcer management long before achlorhydria developed. Healing of the ulcer occurred at variable intervals, usually within a few weeks; in one instance, six months were required for the process to become complete. During this time the acidity decreased slowly, achlorhydria developing in six months; the achlorhydria lasted two months; the acid returned gradually, but the ulcer has not recurred in the subsequent two years.

The hydrochloric acid returned to its previous level in one-third of those who received over 1100 r and in two-thirds of those who received smaller doses. By comparing the incidence of recurrence in patients treated with radiation with that in patients who did not receive such treatment, it seems clear that radiation significantly lowers the frequency of recurrence in gastric and duodenal ulcer; the data with regard to jejunal ulcer are incomplete.

#### CONCLUSIONS

1. Irradiation of the acid secreting portions of the stomach is a valuable procedure in the treatment of peptic ulcer, the effect being proportional to the reduction in gastric secretion.

2. There is no correlation between the effect of treatment and the age of the patient or the duration of the disease prior to irradiation.
3. There is a higher incidence of post radiation achlorhydria in patients with gastric ulcer than in those with duodenal or jejunal ulcer.
4. The achlorhydria varies in duration from a few days to as long as 8 years.
5. Ulcer pain disappears during achlorhydria.
6. Irradiation achlorhydria does not produce symptoms.
7. Achlorhydria of 3 months duration invariably results in healing of the ulcer.
8. Recurrence of the ulcer is preceded by reappearance of acid gastric secretion.
9. The incidence of recurrence is definitely lowered by irradiation.

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## RADIATION THERAPY IN PEPTIC ULCER: A STUDY OF SELECTED CASES

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The effect of roentgen irradiation of the acid-secreting portions of the stomach upon gastric secretion and the healing and recurrence of peptic ulcer, has been described in previous publications.<sup>1, 2</sup> The basic premise is that acid gastric juice is essential for the production of peptic ulcer and for its chronicity; any procedure which reduces acidity decreases the digestive power of the gastric content and thus favors the process of healing. Roentgen irradiation exerts a variable and unpredictable effect upon gastric secretion. In certain patients the depression is profound and prolonged. For this reason, it seems worth while to supplement the statistical analysis with a description of some of the more dramatic results and a consideration of some of the failures.

### GASTRIC ULCER

Case 1 (Figs. 1, 2). A. K., Unit #148736, female, first developed ulcer distress in 1903 at the age of 33. After a period of nearly two years the distress subsided and did not recur until she was 50 (1923). Since then there have been recurrent episodes of ulcer pain. In 1930, roentgen examination of the stomach elsewhere reported "a scar in the stomach". Antacid therapy was instituted and continued for nearly eight months with complete relief; however, the pain recurred in 1934. In April 1935, the gastrointestinal symptoms became worse, with almost continuous pain, nausea and vomiting, a loss of 15 pounds in weight, and tarry stools. In the spring of 1936, when seen by us for the first time, the roentgenologic and gastroscopic examinations both disclosed benign ulcer on the lesser curvature of the stomach (Fig. 1). A rigid antacid program was instituted; the symptoms subsided completely; x-ray and gastroscopy demonstrated a progressive, slow decrease in size of the ulcer with complete disappearance in March 1937. The ulcer was again present from May 1937 to January 1938, disappearing only to recur in July 1938. The fluctuating course of the ulcer, its variation in size, disappearance and recurrence were well demonstrated by gastroscopy. In January 1943, the ulcer crater appeared very shallow and was estimated as 2 mm. in diameter. Antacid therapy was continued and the patient's symptoms were controlled except for brief periods of distress. From October 1942 to March 1945, she had occasional episodes of epigastric distress relieved by alkali. In May 1945, the patient complained of abdominal distress, vomited several times at night, felt weak, and lost 25 pounds in weight. She was hospitalized for three weeks in April 1946. X-ray disclosed an ulcer 1.5 cm. in

\* Presented before the American Gastroenterological Association in Atlantic City, May 1, 1948.

diameter and 1 cm. in depth and a pronounced hour glass constriction; gastroscopy showed an ulcer 1.5 cm. in diameter, located below the constricted area with no infiltration of the adjacent mucosa. In addition to the routine medical management, the patient was given a course of radiation therapy, 1600 r depth dose in fifteen days directed to the fundus of the stomach. This was followed by achlorhydria persisting

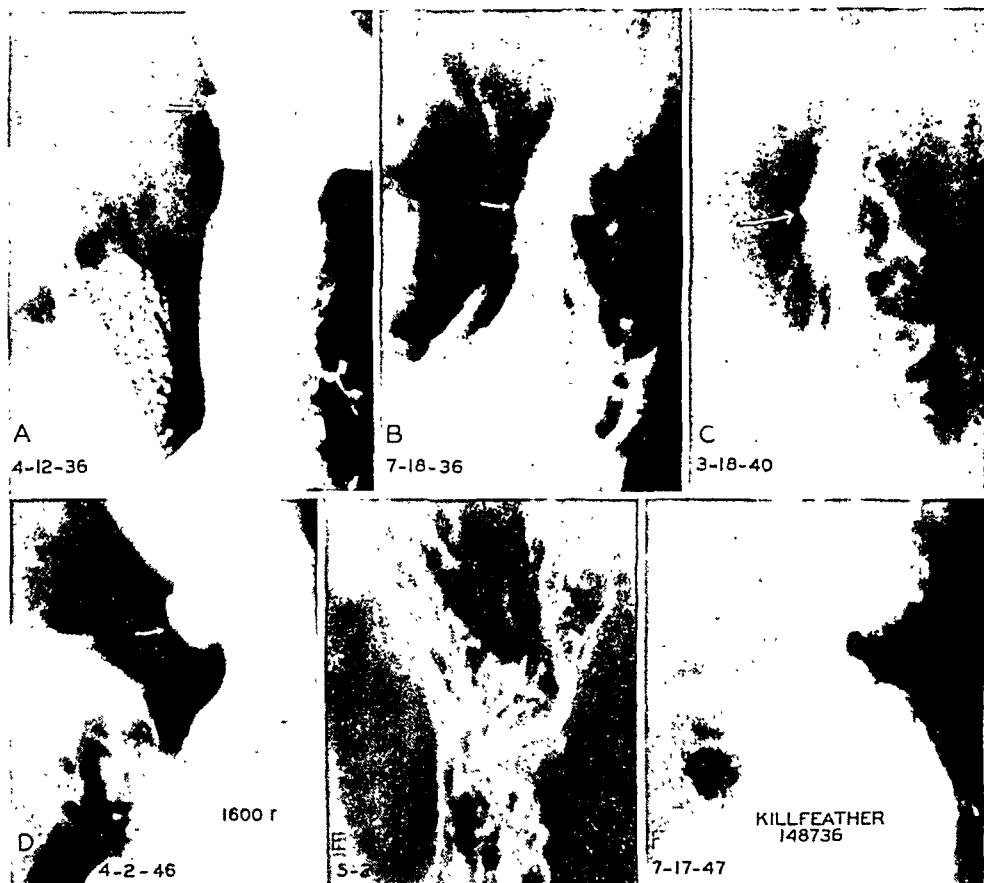


FIG. 1. CASE 1. RECURRENT GASTRIC ULCER, A, B, C, AND D, (38 X-RAY AND 95 GASTROSCOPIC EXAMINATIONS) WITH COMPLETE HEALING FOUR WEEKS AFTER RADIATION (1600 r IN APRIL 1946) (E) PRODUCING COMPLETE ACHLORHYDRIA: NO RECURRENCE TO DATE

to the present time. The ulcer was not seen three weeks after completion of radiation therapy and has not been visualized subsequently. There have been no symptoms; antacid therapy has been discontinued. In March 1948, the patient was still in excellent health. During these ten years of observation she has undergone 38 roentgen examinations, 95 gastroscopies, and 92 histamine tests. Radiation therapy produced a prolonged achlorhydria and a dramatic cure of the ulcer.

Case 2 (Fig. 3). A. S., Unit #10239, a white male, aged 26 in 1928, developed gnawing epigastric pain one to two hours after meals relieved by food and alkali, recurring periodically until admission in the summer of 1941. Roentgen examination

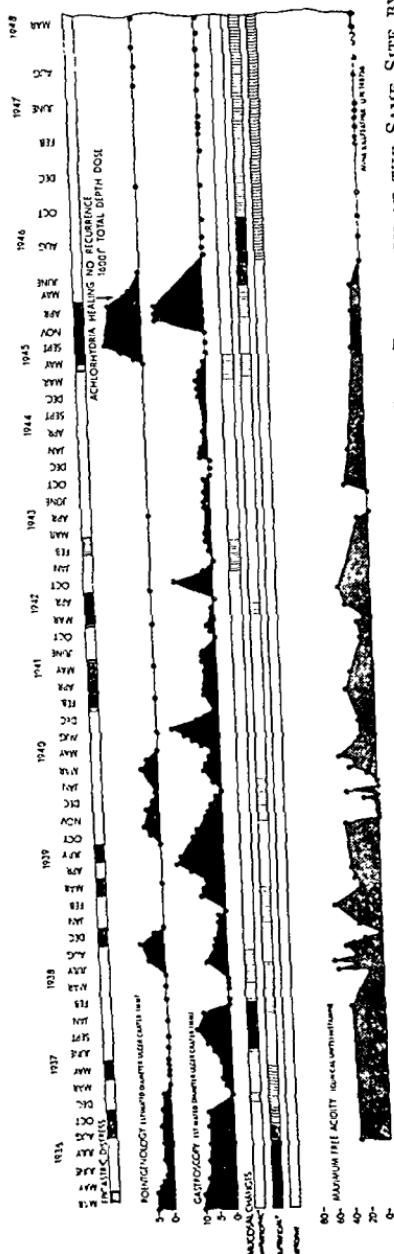


FIG. 2. CASE 1. GRAMMIC DEPICTION OF A CHRONIC RECURRING GASTRIC ULCER AS SEEN REPEATEDLY AT THE SAME SITE BY X-RAY AND GASTROSCOPY

Each dot represents an examination. Following the development of achlorhydria in the spring of 1946 the ulcer healed and has not recurred.

disclosed a large benign ulcer in the middle of the lesser curvature of the stomach, confirmed by gastroscopy. The maximum free acidity (histamine) was 50 clinical units. A modified Sippy regimen was prescribed. Radiation therapy was given decreased following irradiation, and achlorhydria was noted on January 12, 1942. The symptoms disappeared promptly; the ulcer healed completely in six weeks, as

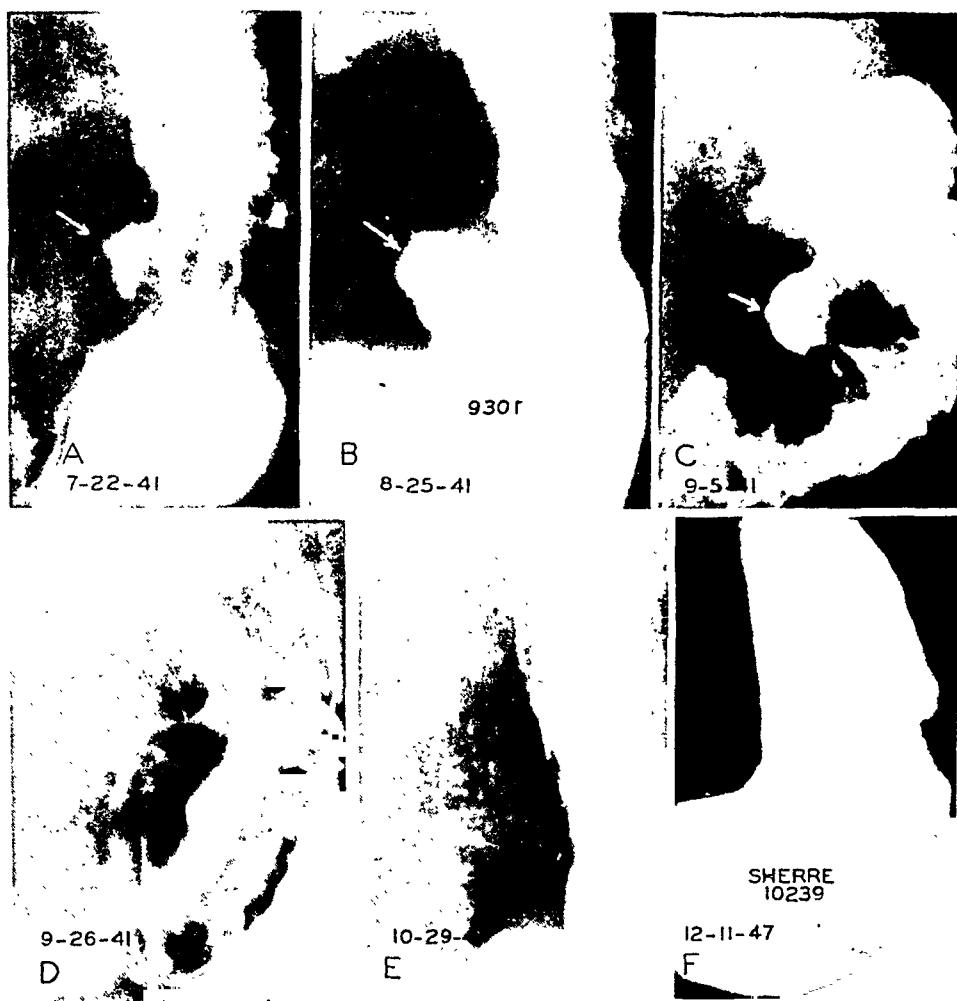


FIG. 3. CASE 2. LARGE GASTRIC ULCER WITH DRAMATIC HEALING 6 WEEKS AFTER RADIATION THERAPY (8-23-1941, 930 r TOTAL DEPTH DOSE) NO RECURRENCE TO DATE (7 YEARS)

shown by repeated roentgenologic and gastroscopic examinations; there has been no recurrence to date (April 1948), despite the fact that since 1946 the free acidity has oscillated from 82 to 111 clinical units.

Case 3 (Figs. 4, 5). A. C. P., Unit #155744, a housewife, in 1932, at the age of 41, experienced gnawing epigastric pain two hours after meals, relieved by milk, cream, and alkali. An ambulatory program of ulcer management was instituted with marked relief. However, the epigastric pain recurred intermittently. In July 1936,

x-ray examination of the stomach disclosed a 2 mm. ulcer on the lesser curvature. The maximum free acidity (histamine stimulation) was 15 clinical units. Ulcer management was followed by complete relief of symptoms; the ulcer healed slowly and disappeared entirely on September 9, 1936. In March 1938, a small 3 mm. ulcer again was noted by x-ray; it disappeared by May 23, 1938. A tiny projection on the lesser curvature of the stomach was observed on April 11, 1939. Gastroscopic

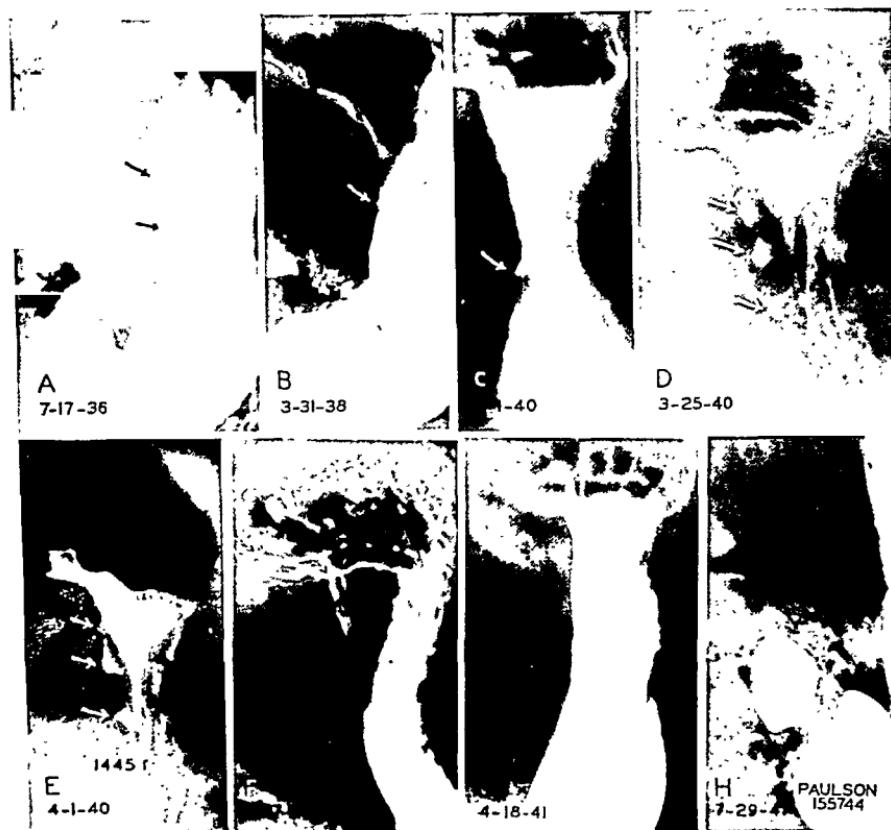


FIG. 4. CASE 3. RECURRENT MULTIPLE GASTRIC ULCERS—COMPLETE HEALING AFTER RADIATION  
NO RECURRENCE SINCE APRIL 1941

examination on June 8, 1939, demonstrated a shallow ulcer at the angulus, several edematous hemorrhagic folds, and moderate atrophy of the mucosa in the anterior wall of the upper two-thirds of the stomach. The ulceration increased in size and on March 15, 1940, was nearly 2 cm. in diameter as seen by x-ray. On March 22, 1940, gastroscopy disclosed an ulcer estimated as 1 cm. long and 3 mm. wide with edematous, reddened borders. Three days later x-ray revealed three gastric ulcers on the upper lesser curvature of the stomach, arranged in a linear fashion. On April 1, 1940, the ulcerations were still present but were smaller. The free acidity had oscillated from 15 to 60 clinical units between 1936 and 1940. From April 5, 1940,

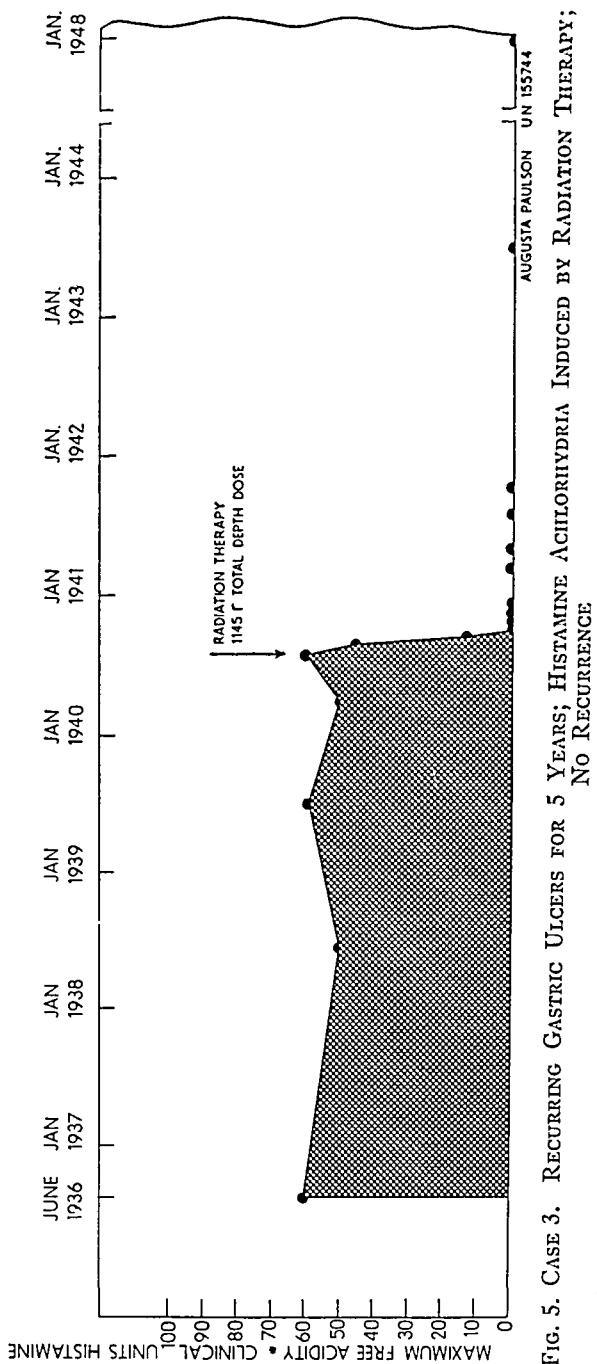


FIG. 5. CASE 3. RECURRING GASTRIC ULCERS FOR 5 YEARS; HISTAMINE ACHLORHYDRIA INDUCED BY RADIATION THERAPY;  
No Recurrence

Each dot represents a histamine test.

to April 16, 1940, radiation therapy was given, with a total dose of 1445 r. On April 19, 1940, the free acidity decreased to 45 clinical units; on April 30, the maximum was 12 clinical units. No free acid was recorded after histamine stimulation on May 13, 1940. On June 17, 1940, all the ulcers had disappeared; there has been no recurrence as indicated by symptoms, gastroscopy, or x-ray. Gastroscopic examinations consistently have disclosed an extensive, diffuse atrophy of the mucosa. This case again illustrates prompt healing after radiation therapy with no recurrence during a period of achlorhydria now of eight years duration.

Of 50 patients with gastric ulcer treated for one month or more with the standard medical antacid regimen and roentgen irradiation there were 5 in whom complete healing, as evidenced by gastroscopic and roentgen examination, did not occur. One of these with a history of seven years duration received treatment in November 1942. The ulcer located on the lesser curvature decreased in size in the next six months but did not disappear entirely. When the patient returned in May 1945, the lesion was still present. The gastric free acidity had not been lowered appreciably. In May 1945, a second course of therapy was followed by complete healing. A second patient, a 43-year-old white male with known diabetes mellitus for three years, an ulcer history of eleven years duration, and an ulcer on the lesser curvature, well visualized gastroscopically, had a gastric free acidity between 60 and 70 clinical units. He was treated with a strict medical management for three years. The ulcer healed almost completely, but, for nearly a year a very small outpocket of the therapy was given, but still the ulcer failed to heal completely. New studies of gastric secretion were made immediately thereafter, but in March 1945 the presence of acid gastric juice was demonstrated. The third patient, a 50-year-old white male with an ulcer on the lesser curvature received roentgen irradiation in May 1945. The acidity was lowered very slightly. The ulcer decreased in size, but was still noticeable as a very small pocket in November 1945. Subtotal gastric resection disclosed a small benign ulcer on the lesser curvature. The fourth and fifth patients both had a transitory achlorhydria, lasting less than three months, during which time the ulcers were reduced considerably in size; as the acidity returned, the size of the ulcer increased. Subtotal gastrectomy disclosed a benign peptic ulcer in each instance. Thus of the five failures after radiation, only minimal secretory depression was obtained in three; in two, the achlorhydria was of short duration.

#### DUODENAL ULCER

Case 4 (Fig. 6). B. M., Unit #259542, a housewife, had had periodic episodes of ulcer distress for thirty-five years. In December 1940, she experienced hematemesis and melena. When first seen in 1941, x-ray disclosed a slightly deformed duodenal bulb with a large crater. A histamine test yielded a maximum free acidity of 60

clinical units. A course of radiation with a 1000 r depth dose was given from March 24, 1941, to April 3, 1941. On April 1, 1941, the maximum acidity was 100 clinical units and on April 8, 1941, 150 clinical units. This transitory increase was followed by a marked decrease and finally, in June 1941, achlorhydria was recorded. The achlorhydria lasted only two months; however, the acidity remained low until June 1942, when it reached the preradiation level. The patient was completely relieved of ulcer distress until June 1944, after which she experienced several recurrent episodes. A recurrent duodenal ulcer crater was found by x-ray on January 4, 1945.

#### TRANSITORY DECREASE ACID SECRETION-HEALING-RECURRENCE-DUODENAL ULCER

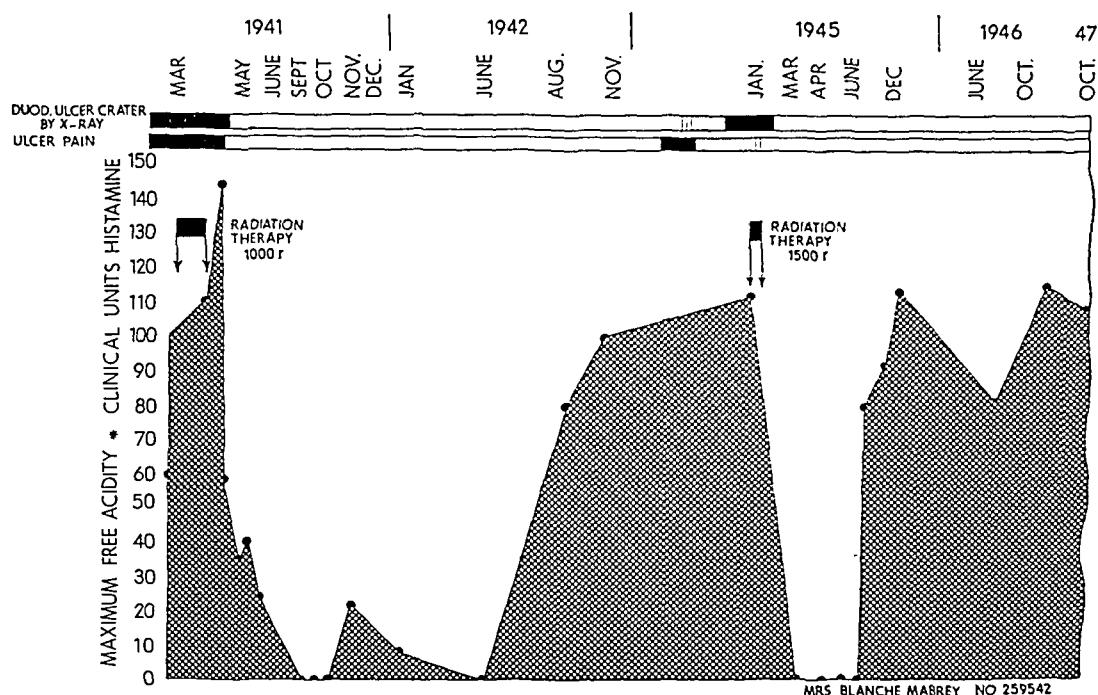


FIG. 6. CASE 4

A second course of therapy with a total depth dose of 1500 r was given from January 16, 1945, to January 26, 1945: achlorhydria again developed lasting three months; the acidity subsequently rose to its previous level. Since 1945, however, the patient has been entirely free of distress; x-ray has shown no recurrence of the ulcer. As depicted in Fig. 6, healing of the ulcer occurred on two occasions after radiation therapy producing each time a brief achlorhydria.

Case 5 (Fig. 7). F. D., Unit #198241, a white male first experienced epigastric distress at the age of 25 in 1935. This pain occurred an hour or so after meals, was relieved by taking food or alkali and by vomiting. The patient was admitted as an emergency on May 13, 1938, because of severe pain. At operation a perforated duodenal ulcer 6 mm. in diameter was found; the perforation was closed; recovery

was uneventful. A histamine test on June 2, 1938, disclosed a maximum acidity of 120 clinical units. The patient received radiation therapy, 1188 r in six days. This was followed by a progressive decrease in acidity ranging between 0 and 34 clinical units in the following five years. The patient had had no recurrence when last seen in 1946. In this instance, the perforated ulcer was repaired surgically, but its failure to recur in the subsequent eight years may be related to the prolonged secretory depression following the radiation therapy (Fig. 7).

**Case 6 (Fig. 8).** Mrs. G. W., Unit #78083, a female aged 46, had experienced ulcer distress periodically since 1930, despite medical management. X-ray on February 28, 1933, disclosed a duodenal ulcer with deformity and stenosis. She was placed on a strict ulcer management including aspiration of the stomach at

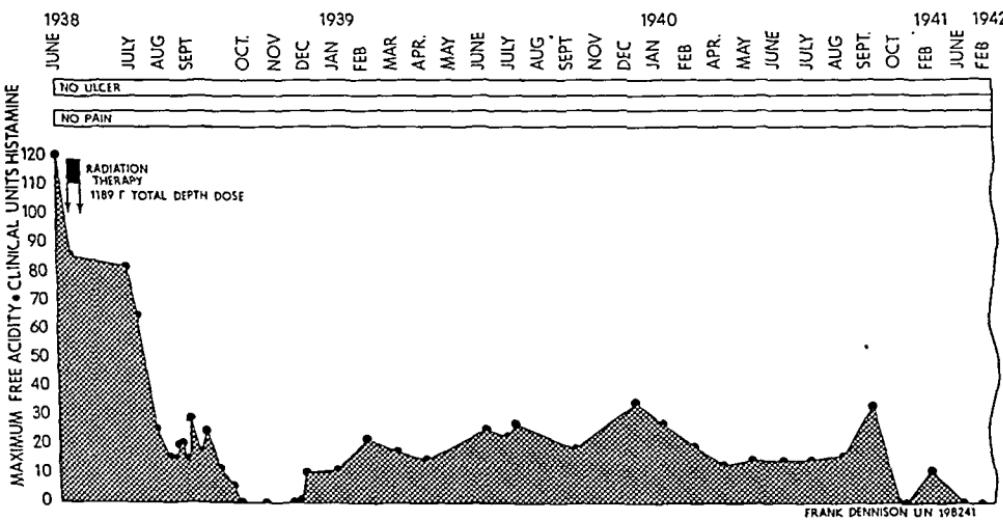


FIG. 7. CASE 5. PROLONGED DEPRESSION OF GASTRIC SECRETION FOLLOWING ROENTGEN IRRADIATION WITHOUT RECURRENCE OF DUODENAL ULCER

bedtime; the pain was relieved. However the symptoms recurred and because of the stenosis, a gastroenterostomy was performed on October 10, 1933. This was followed by complete relief for nearly two years. On May 11, 1936, she suddenly experienced nausea and vomiting, passed dark stools, became weak, and re-entered the hospital; a diagnosis of a jejunal ulcer with hemorrhage was made. Under medical management she improved and was discharged on June 15, 1936. For nearly two months she felt well, but on August 16, 1936, she again passed several tarry stools and had an emesis of coffee-colored material. She re-entered the hospital and on August 20, 1936, underwent an operation, at which time the gastroenterostomy was taken down and a resection of the anastomotic ulcer performed. She continued to experience epigastric distress despite this operation. On September 3, 1936, her condition was complicated by a coronary occlusion. The patient was discharged free of distress on ulcer management on October 11, 1936. She remained

well until April 9, 1937, at which time she again experienced epigastric pain, necessitating hospitalization. Again she was relieved, but in September 1937 the pain recurred and x-ray examination disclosed a duodenal ulcer crater. The gastric free acidity was 110 clinical units. Radiation therapy was given from September 27 to October 13, 1937. Achlorhydria was present two weeks after completion of the radiation. The patient was entirely relieved from ulcer distress and has remained so until the present, a period of more than ten years. Repeated x-ray examinations

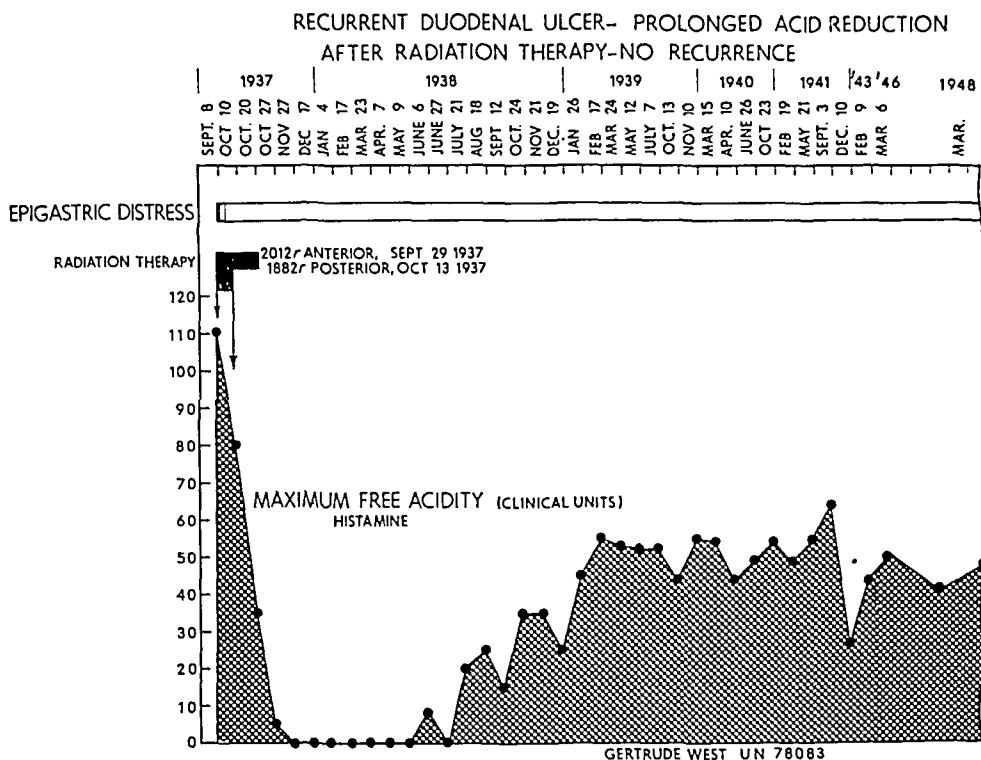


FIG. 8. CASE 6

have shown a persistent deformity of the duodenal bulb but no crater. The achlorhydria continued until May 1938, when again free hydrochloric acid was present. The free acidity since then has varied from 25 to 62 clinical units, approximately one-half as high as it was before radiation. In this instance, an "intractable" duodenal ulcer healed after radiation therapy which produced an achlorhydria of several months duration and a permanent reduction in gastric secretion.

#### JEJUNAL ULCER

Relatively few cases of jejunal ulcer have been subjected to radiation therapy. The results have often seemed surprisingly good, but on the other hand the incidence of ultimate recurrence has been high.

## DISCUSSION

The purpose of this paper has been to focus attention upon the occasional dramatic effect of radiation therapy upon the course of chronic peptic ulcer and to correlate this effect with alterations in gastric secretion. It has been found easier to depress gastric secretion in patients with gastric ulcer than in patients with duodenal or jejunal ulcer. This observation is not surprising in view of the finding<sup>3</sup> that the fasting secretory rate, in terms of milligrams of hydrochloric acid per unit of time, is, on the average, approximately four times as great in patients with duodenal ulcer as it is in those with gastric ulcer. The explanation of this striking difference is not apparent. The secretory mechanism in patients with gastric ulcer is more easily inhibited by radiation therapy. Thus, achlorhydria resulted in 32 (68 per cent) of 47 patients with gastric ulcer, as contrasted with 106 (30 per cent) of 352 patients with duodenal ulcer receiving comparable amounts of radiation. There is some evidence, also, that in patients with gastric ulcer the mucosal cells are more easily injured and that atrophy of the mucosa is a more frequent sequel.

The ultimate value of radiation therapy in peptic ulcer and the ultimate effect of the procedure on the gastric mucosa have yet to be determined.

## CONCLUSIONS

Roentgen irradiation of the acid-secreting portions of the stomach may produce a profound depression of gastric secretion persisting for variable periods of time. The effect on the course of the ulcer depends upon the degree and duration of the secretory depression.

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## EFFECT OF ROENTGEN IRRADIATION ON THE GASTRIC MUCOSA\*

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### INTRODUCTION

The purpose of this report is to describe the gastroscopic appearance of the gastric mucosa following roentgen irradiation in man, and, also, to comment briefly upon the subsequent histologic changes in the stomach.

In recent years, roentgen irradiation of the fundus and body of the stomach for the purpose of reducing gastric secretion has been included in our program of ulcer management<sup>1</sup>. The total quantity of radiation has varied from 1100 to 2500 r, applied in divided doses. The free acid in the gastric content has been measured at frequent intervals by the standard histamine test. Gastroscopy has been performed before and after irradiation in 65 patients and, after therapy, in an additional 55 cases, a total of 504 gastroscopic examinations being made. The duration of endoscopic observation has varied, extending, in several instances, for as long as 10 years.

### RESULTS

The characteristic gastroscopic features consisted of redness and edema of the mucosa, hemorrhage and adherent exudate (Plate I). These changes were noted in 75 of the 77 patients examined one week to three months after irradiation, at a time when the gastric acidity was significantly reduced. They were already present in 9 of 25 patients of the above group gastroscoped earlier than one week after the conclusion of therapy (Table 1). These features were not evident, however, in 9 individuals in whom the secretion did not diminish, nor in 14 patients gastroscoped later, at a time when the initial effects of radiation had subsided and the acidity had returned to original levels.

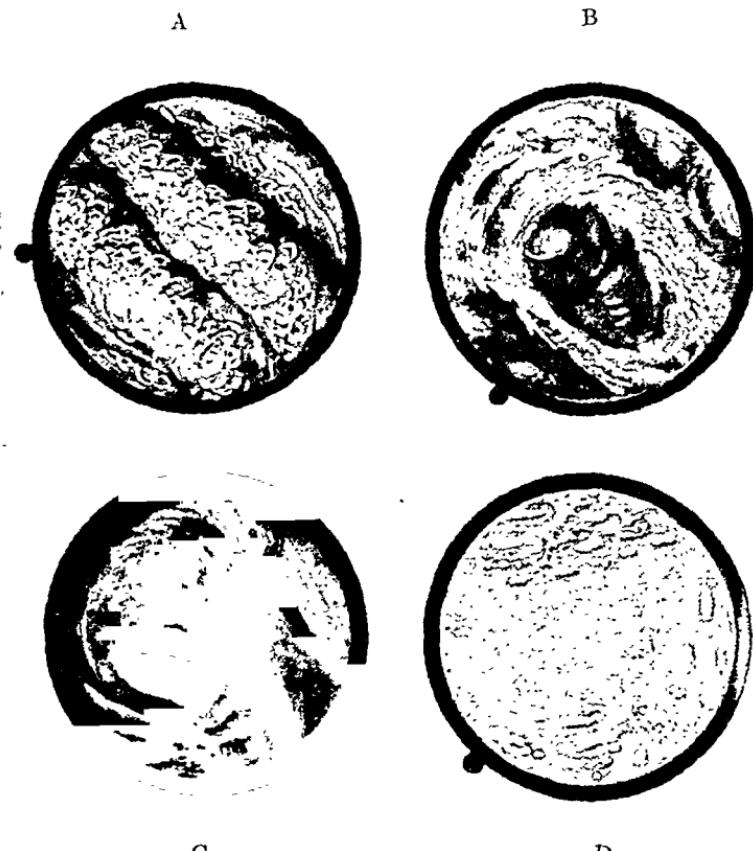
### IRRADIATION OF NORMAL-APPEARING GASTRIC MUCOSA

The mucosa presented a normal appearance in 18 patients prior to therapy. Gastritis was apparent in 14 of these, seven days or more after irradiation (Table 2); the free acidity decreased significantly in each. The mucosa remained normal in 4 cases; gastric secretion had not diminished in 3; the fourth patient was gastroscoped after the acidity had returned to original levels. The following case is illustrative:

*Case 1.* E. B. (Unit No. 177206) (Fig. 1), a 50 year old male was admitted on June 15, 1937, with a history of ulcer distress for 7 years. The maximum free acidity

\* Presented at the Fourth Annual Meeting, American Gastroscopic Society, May 2, 1948.

(histamine) was 110 clinical units. Roentgen and gastroscopic examinations demonstrated an apparently benign ulcer on the lesser curvature of the stomach, at the angulus. A total of 1758 r (depth dose) was applied fractionally to the fundus and body of the stomach during the period June 27 to July 2, 1937. Anacidity developed



## PLATE 1

A. Edema of folds of greater curvature, with adherent "foamy" exudate—20 days after gradual application of total of 1560 r to fundus and body of stomach.

B. Same patient—marked hyperemia and edema of rugae along greater curvature, with adherent exudate.

C. Hyperemia, edema and superficial ulceration just above angulus—14 days after gradual application of 1764 r.

D. Marked atrophy of mucosa and patchy exudate—17 months after gradual application of 1760 r to stomach; prolonged post-irradiation anacidity.

3 months later, with complete healing of the ulcer. Gastroscopy disclosed hyperemia, edema and small quantities of adherent, whitish exudate in the antrum and lower portion of the body of the stomach. Similar findings were noted 5 months after irradiation; in addition, a shallow, elliptical ulceration was observed at the angulus; the ulceration healed within one month. The anacidity persisted until September 1938 (14 months after therapy), when a peak of 15 clinical units of acid was recorded.

TABLE 1  
*Mucosal changes after irradiation*  
(Within 1 week)

APPEARANCE OF THE MUCOSA	NO. CASES	PER CENT
Unchanged.....	16	64
Altered.....	9	36
Edema.....	7	
Hyperemia.....	5	
Hemorrhages.....	5	
Adherent exudate.....	4	

TABLE 2  
*Effect of irradiation upon gastroscopically normal mucosa*  
(1 to 12 weeks after radiation—18 cases)

GASTROSCOPIC FINDING	NO. CASES	PER CENT
Hyperemia.....	9	50
Adherent exudate.....	8	44
Edema.....	5	28
Hemorrhages.....	4	22
Atrophy.....	2	11
Erosions.....	2	11
Cobblestone-like.....	1	6
Normal.....	4	22

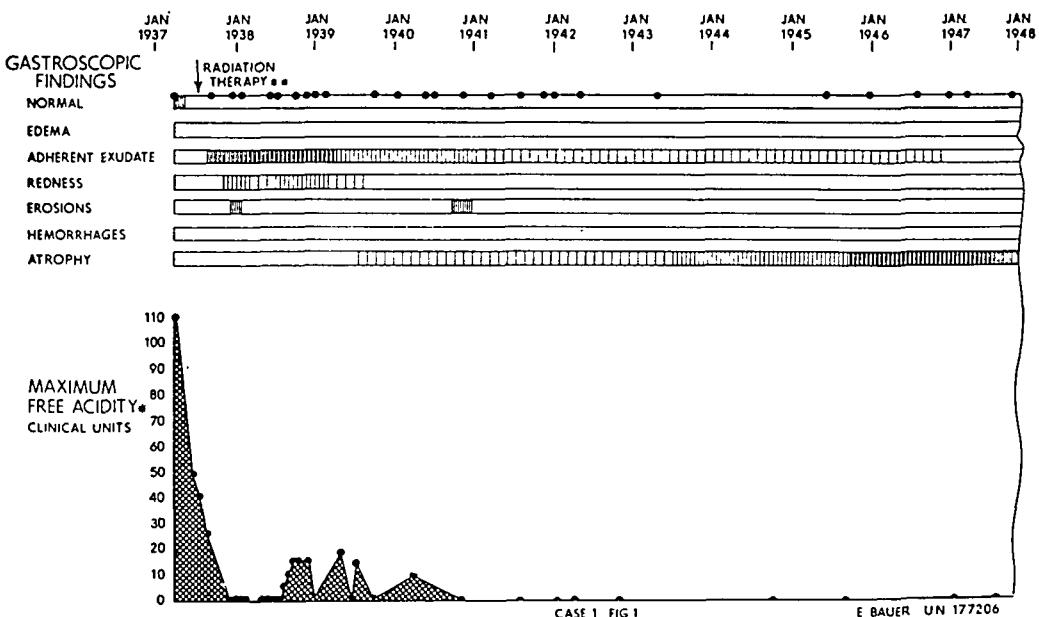


FIG. 1. Normal mucosa—post irradiation inflammation (exudate—hyperemia—erosions). Atrophy—histamine anacidity—8 years.  
Each dot represents one examination, the vertical lines indicate severity of gastroscopic change, the greater the distance between lines the less the severity, empty block indicates absence of particular findings.

\* Histamine stimulation.

\*\* 1785 r total depth dose given in 6 days.

An acidity reappeared in January 1939. Gastroscopy now revealed in addition to the hyperemia and exudate, moderate atrophy of the gastric mucosa. The anacidity has persisted to the present time. Numerous gastroscopies have demonstrated atrophy and occasional patches of adherent exudate. The patient remains free of symptoms.

#### IRRADIATION OF "COBBLESTONE-LIKE" MUCOSA (HYPERTROPHIC GASTRITIS)

A nodular, velvety, cobblestone-like mucosa was observed gastroskopically prior to irradiation in 19 patients. Hyperemia, edema, and adherent exudate were noted subsequently in the 15 in whom the acidity was reduced significantly (Table 3); there was no appreciable change in 4. In one, the secretion had been unaffected at the time of gastroscopy, 2 weeks after therapy. In the

TABLE 3  
*Effect of irradiation upon "cobblestone-like" mucosa*  
 ("Hypertrophic Gastritis")  
 (1 to 12 weeks after radiation—19 cases)

GASTROSCOPIC FINDING	NO. CASES	PER CENT
Adherent exudate.....	15	78
Hyperemia.....	14	73
Edema.....	9	47
Cobblestone-like .....	4	21
Hemorrhages.....	2	10
Erosions.....	1	5
Atrophy.....	0	0
Normal.....	0	0

second, the acidity decreased only temporarily. In the third, the pre-irradiation changes persisted for 7 months and then subsided. In the fourth, the "hypertrophic" appearance persisted, although the gastric acidity decreased by 50 percent. Eleven of the 19 patients were observed subsequently for periods of 1 to 10 years; the mucosa became atrophic in 8, normal in 2, and was unchanged in one. The following cases are representative of this group:

**Case 2.** J. W. (Unit No. 363310) (Fig. 2), a 55 year old male had experienced ulcer distress for 5 years at the time of his admission in August 1945. The maximum free acidity was 74 clinical units. Roentgen examination revealed large gastric rugae and a duodenal ulcer crater. Very large, stiffened folds, estimated as 2 to 3 cm. in height, and a moderately hyperemic, coarsely nodular mucosa were observed gastroskopically, interpreted as "giant hypertrophic gastritis". From September 28 to October 13, 1945, 1710 r were directed to the fundus and body of the stomach. Three weeks later the rugae appeared edematous, reddened and covered with exudate. Eight months after irradiation (June 1946) gastroscopy disclosed a pale mucosa with occasional accumulations of yellowish-white adherent exudate; the rugae now were

normal in size. Fourteen months after therapy (December 1946) the mucosa appeared moderately atrophic. Histamine-anacidity persisted until November 1946 when 31 clinical units of free acid were obtained; the acidity subsequently ranged from 26 to 40. Gastroscopy on February 19, 1948 (2 years and 4 months after irradiation) disclosed only mild atrophy in the upper portion of the stomach. The patient continues in excellent health.

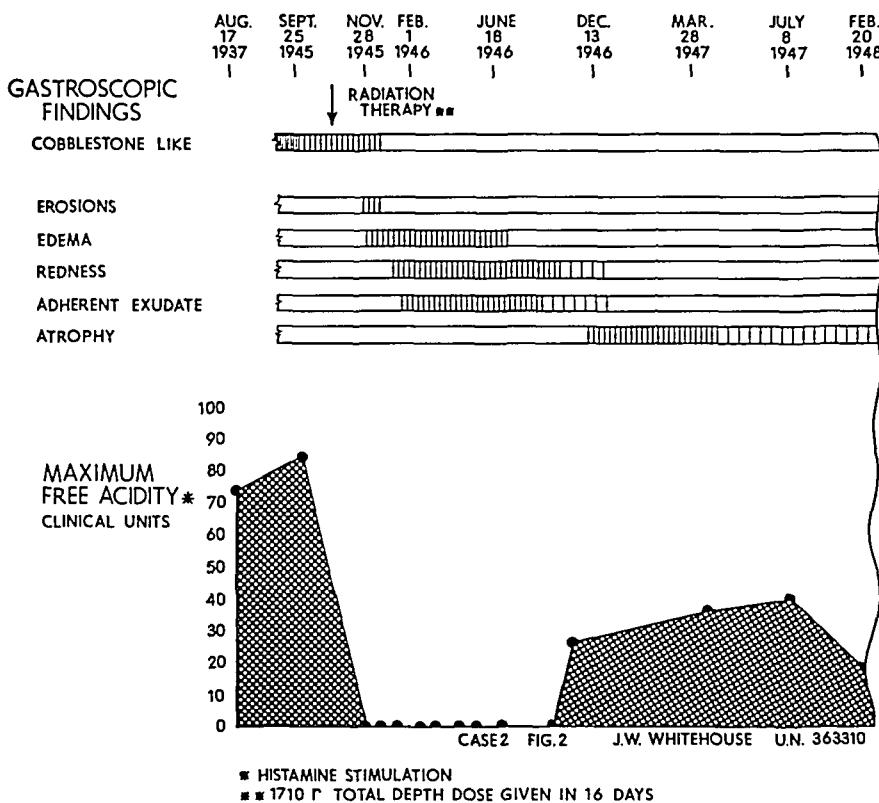


FIG. 2. Cobblestone like mucosa—post irradiation inflammation (edema, hyperemia, adherent exudate, erosions)—atrophy.

Each dot represents one examination, the vertical lines indicate severity of gastroscopic change, the greater the distance between lines, the less the severity. Empty block indicates absence of particular findings.

**Case 3.** J. F. (Unit No. 188928), a 31 year old male was first seen in December 1937, having experienced ulcer distress for 4 years. The roentgen and gastroscopic examinations demonstrated a small, apparently benign ulcer, located just above the angulus; the mucosa presented a cobblestone-like appearance and contained large hemorrhages. The maximum acidity was 122 clinical units. From December 31, 1937 to January 12, 1938, a total of 2952 r (measured in air) was directed to the fundus and body of the stomach. At gastroscopy on January 10 the original changes were limited now to the small area of two folds; a large quantity of adherent exudate was present in the upper portion of the stomach. Two weeks after irradiation, the examination disclosed mild nodularity of the mucosa of the antrum, and hemorrhages

and exudate in the upper portion of the stomach. One month later the mucosa presented a dull, velvety, cobblestone appearance. The maximum acidity at this time (February 1938) was 45; a peak of 100 clinical units was obtained in April 1939. In September 1947 the roentgen examination demonstrated a normal stomach and duodenum. Gastroscopy revealed a mildly atrophic mucosa and a very small quantity of exudate. The patient has remained well.

*Case 4.* J. A. (Unit No. 308204), a 59 year old male had had ulcer symptoms for 11 years at the time of his admission in April 1942. Roentgen examination disclosed ulcer craters on the lesser curvature of the stomach and in a deformed duodenal bulb. From May 27 to June 28, 1943, 1815 r were applied to the fundus and body of the stomach. Histamine anacidity developed after two weeks. The ulcers healed and were not demonstrable one month later. Three gastroscopies prior to irradiation revealed, in addition to the gastric ulcer, reddened, edematous and stiffened rugae. The folds, three and one-half months later, were redundant, but the mucosa otherwise appeared normal. The maximum acidity in August 1947 was 40 clinical units. The patient remains free of symptoms.

#### IRRADIATION OF ATROPHIC GASTRIC MUCOSA

A diffusely atrophic mucosa was observed prior to irradiation in 4 patients. Subsequently, hyperemia and adherent exudate were noted in 4, edema in 3 and hemorrhages in 2 cases. Gastroscopic-observation in 3 of the group extended for more than one year. The acute inflammation subsided, the atrophy continued, and, in fact, increased. The following case is illustrative:

*Case 5.* A. C. P. (Unit No. 155744) (Fig. 3) a 45 year old housewife was first seen in July 1936, having noted ulcer symptoms for 4 years. A small ulcer was observed roentgenologically on the lesser curvature of the stomach. The maximum free acidity was 15. The ulcer healed during antacid therapy, reappeared in March 1938 and again healed. In April 1939 an ulcer crater was demonstrated by X-Ray on the lesser curvature of the stomach. Gastroscopy in June 1939 revealed a shallow ulcer at the angulus, several edematous hemorrhagic folds and moderate atrophy of the anterior wall in the upper two-thirds of the stomach. The crater disappeared, but in March 1940, a large ulcer, approximately 2 cm. in diameter, was again noted; shortly thereafter, 3 ulcerations arranged in linear fashion were demonstrated by X-Ray on the upper portion of the lesser curvature. The free acidity between 1936 and 1940 ranged from 15 to 60 clinical units. From April 5 to April 16, 1940, 1445 r were directed to the fundus and body of the stomach. Anacidity developed one month later, persisting to the present time. The ulcerations healed completely within 2 months and have not recurred. Ten subsequent gastroscopies consistently have demonstrated marked atrophy of the entire mucosa.

It should be noted that there have been no untoward late effects after irradiation in this patient observed for 8 years and in Cases 1 and 3 followed for 10 years.

## IRRADIATION OF DIFFUSELY INFLAMED MUCOSA

A diffuse gastritis of the "superficial" type was observed prior to irradiation in 4 patients. The appearance of the mucosa subsequently was indistinguishable from that noted at the control examination.

## RELATION BETWEEN SEVERITY OF GASTRITIS AND REDUCTION IN GASTRIC ACIDITY

As indicated above, the intensity of the inflammation was directly proportional to the decrease in histamine-stimulated secretion. "Irradiation gas-

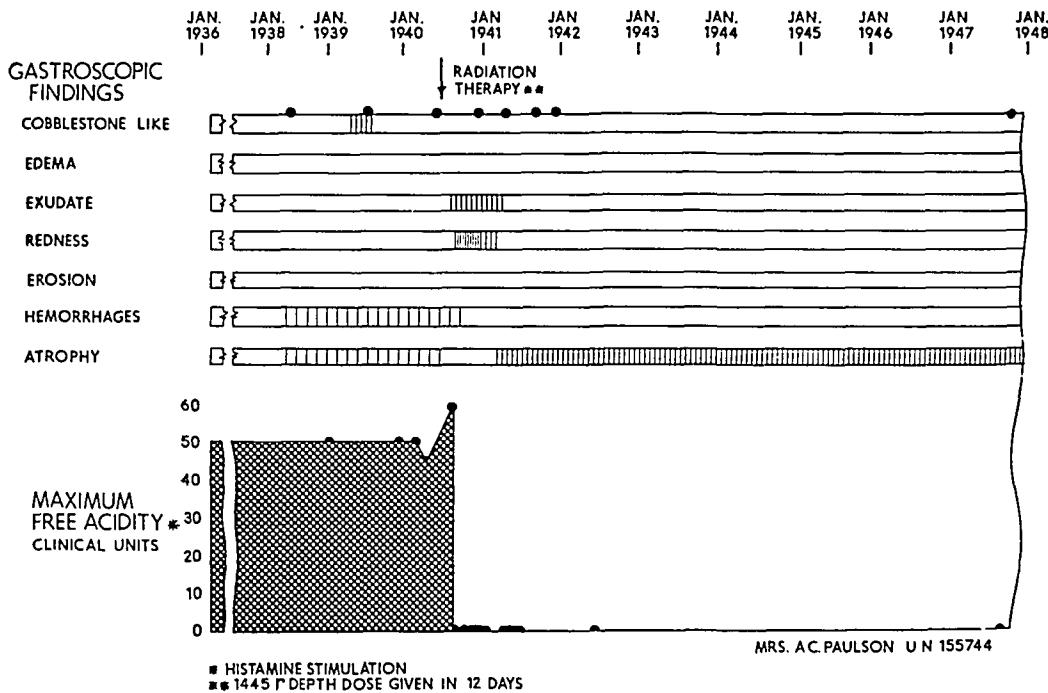


FIG. 3. Post irradiation exudate and hyperemia—atrophy—histamine anacidity 7 years.  
Each dot represents one examination, the vertical lines indicate severity of gastroscopic change, the greater the distance between lines, the less the severity. Empty block indicates absence of particular findings.

tritis" was not observed in 9 individuals in whom the acidity was not reduced, whereas, severe inflammation was noted in all of 22 patients with post-irradiation anacidity, examined 1 to 6 months after therapy (Table 4). Atrophy of the mucosa was present in all of 8 patients with anacidity of 2 or more years duration (Table 5), having been noted in 2 of this group prior to irradiation.

## PATHOLOGICAL FEATURES

The histologic changes produced by roentgen irradiation of the stomach and intestines in animals, have been described in detail by Engelstad<sup>4, 5</sup> and by Warren and Friedman<sup>2</sup>, among others<sup>3, 6-37</sup>. These findings consist of

cellular degeneration, hyperemia, edema, increased transudation and leukocytic infiltration, with ulceration 1 or 2 months after the irradiation. The major effect occurs in the mucosa, although all elements of the gastric wall are involved. The severity of the changes is directly proportional to the intensity of the radiation. In rabbits, 250 to 500 r induced relatively mild alterations, whereas 2000 or more r produced ulceration with perforation and hemorrhage and a very high mortality as a result of anorexia and inanition<sup>5, 6</sup>. The changes

TABLE 4  
*Mucosal changes in histamine achlorhydria*  
(1 to 6 months—22 cases)

GASTROSCOPIC FINDING	NO. CASES	PER CENT
Adherent exudate.....	22	100
Hyperemia.....	18	81
Edema.....	11	50
Hemorrhages.....	4	18
Atrophy.....	4	18
Erosions.....	3	13
Normal.....	0	0
Cobblestone-like.....	0	0

TABLE 5  
*Mucosal changes in prolonged histamine achlorhydria*  
(Longer than 2 years—8 cases)

GASTROSCOPIC FINDING	NO. CASES	PER CENT
Atrophy.....	8	100
Adherent exudate.....	4	50
Hemorrhages.....	2	25
Hyperemia.....	1	12
Erosions.....	0	0
Normal.....	0	0
Cobblestone-Like ("Hypertrophic") .....	0	0

were much less intense after fractional applications than following the single administration of a similar quantity of radiation. Comparable observations have been made in man. Brick<sup>38, 39</sup> described perforating ulcers in 5 patients previously without gastric disease, given 5000 to 6000 r. This amount of radiation is far in excess of the gradually administered 1100 to 1800 r depth dose, utilized in the present study. Among more than 880 patients so treated, gastric erosions were noted gastroscopically in 3 and rapidly healing superficial ulcerations in only two instances (Fig. 4).

Gastric tissue was obtained in 18 previously irradiated patients either by

biopsy (without the use of ligatures or clamps) or by partial resection of the stomach, from one day to three and one-half years later. The time interval in 9 of the 18 cases was 1 to 24 days. Inflammatory changes had been noted gastroscopically in all; histamine-anacidity had been present in 2. The microscopic findings were similar to those described in animals. They included degeneration of occasional epithelial cells, a highly cellular, fibrin-containing exudate, marked infiltration of the entire wall, but especially the mucosa, at first with polymorphonuclear cells and later, plasma cells, lymphocytes, eosinophiles and macrophages; also dilatation of blood vessels and lymphatics,



FIG. 4. Section through gastric mucosa showing a layer of mucus on the surface; mild injury to epithelium only; polymorphonuclear exudation interstitially and in crypts.  $\times 125$ . One day after application of 1692 r in 12 days.

occasional thickening of the endothelium and hyalinization of the media, edema of connective tissue with so-called fibroblast paralysis and degeneration of lymph follicles (Figures 5-9).

The stomach was examined in 5 patients, 7 weeks to 5 months after irradiation. The gastric content contained free acid in all cases. The microscopic changes were relatively slight, consisting chiefly of increased cellular infiltration. Atrophy of the mucosa was observed in 3 cases, having been present gastroscopically prior to irradiation in the two patients examined.

Histologic examination in the remaining 4 cases was made 16 months to three and one-half years after therapy. Free acid was present in each; atrophy

was observed in the one individual gastroscoped before operation. In this patient, a severe hypertrophic gastritis had been observed three and one-half years earlier, followed by atrophy after an initial course of irradiation. The ulcer recurred, a second course of irradiation was given, and a partial gastric



FIG. 5. Section through gastric mucosa showing degeneration of epithelium, particularly the chief cells and the epithelium of the crypts; interstitial exudation with fibrin as well as polymorphonuclear cells; focus of fresh hemorrhage with a very superficial erosion.  $\times 78$ . Five days after application of 1447 r in 19 days.

resection performed three weeks later. Microscopically, there was an acute inflammation superimposed upon an atrophic mucosa, resulting presumably from the initial irradiation. In general, the histologic changes in this group of 4 patients were slight and could not be attributed specifically to the previous therapy.



FIG. 6. Section through gastric mucosa showing an edematous fold with venous and lymphatic telangiectasia; exudation with polymorphonuclear and mononuclear cells.  $\times 30$ . Seven weeks after application of 1600 r in 12 days.



FIG. 7. Extensive but superficial ulceration which, in occasional areas, has penetrated almost to muscle coats.  $\times 12$ . Fifteen days after application of 1200 r in 17 days.

## COMMENT

The foregoing observations indicate that moderate roentgen irradiation of the upper portion of the stomach in man produces an acute inflammation of the entire gastric wall. "Irradiation gastritis" is characterized gastro-



FIG. 8. Same case. Reepithelialization at margin of ulceration; the unusually large non-proliferative fibroblasts suggest so-called fibroblast paralysis.  $\times 375$ .

scopically by hyperemia, edema, hemorrhage and exudation; erosions are infrequent and ulceration is rare. These findings previously had been interpreted as "chronic superficial gastritis"<sup>33, 40</sup>. The present study indicates that the gastritis is neither chronic nor superficial. The gastritis usually becomes evident one week or more after irradiation and may persist in diminishing degree for several months. The severity of the gastritis is directly

proportional to the decrease in gastric secretion. The inflammation usually is transitory and is followed by atrophy, which is consistently present in patients with anacidity of two or more years duration. The nodular, velvety, thickened, cobblestone-like features of "hypertrophic gastritis" usually disappear following roentgen irradiation, the mucosa assuming a normal or mildly atrophic appearance; despite these observations, roentgen irradiation is *not* indicated, in our opinion, for the treatment of hypertrophic gastritis alone.

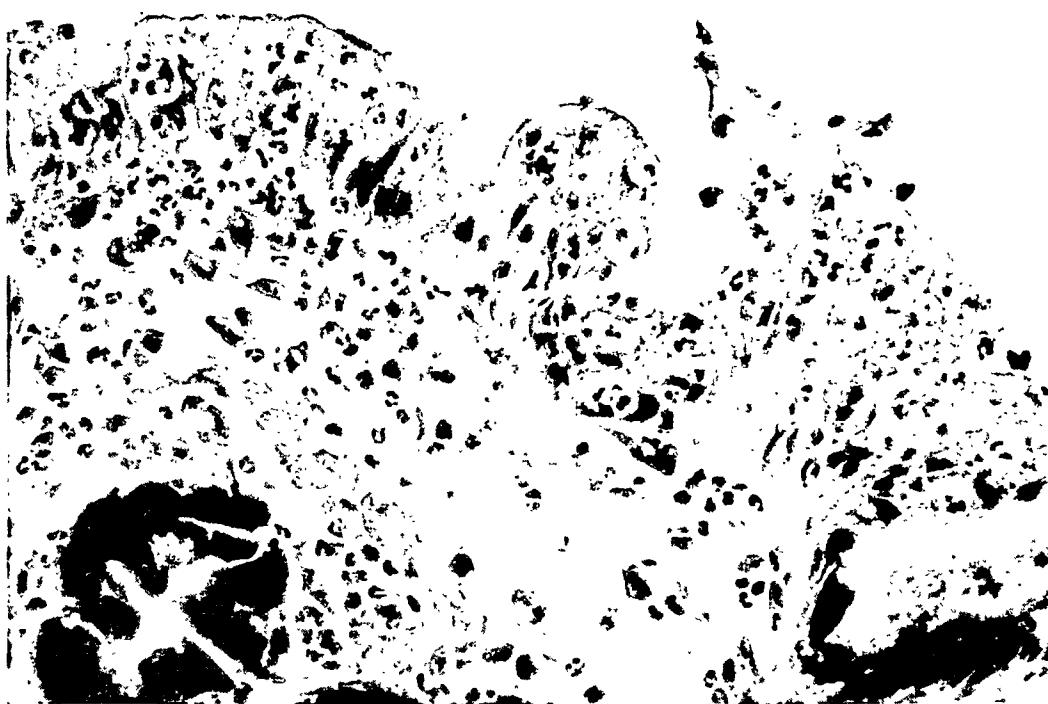


FIG. 9. Same case. Section through gastric mucosa showing polymorphonuclear leukocytes of the exudate in the mucosa and in migration through the epithelium, at some distance from the ulceration.

Histologically, "irradiation gastritis" in man, as in the experimental animal, consists of an acute inflammation, involving all elements of the gastric wall, especially the mucosa. It is characterized by degenerative changes, hyperemia, hemorrhage and increased cellular infiltration; atrophy of the mucosa is a frequent consequence. The inflammatory changes are apparent histologically almost immediately after irradiation; they are less prominent 6 months later, and, except for atrophy, are probably not demonstrable 16 months or more after irradiation. The interpretation of the microscopic findings in human gastric tissue is, of course, complicated by the lack of control observations. The acute changes and the subsequent atrophy coincide with the gastroscopic observations and are, therefore, attributable to the irradiation.

tion. The minor histologic findings noted several months or more after the therapy may or may not be related to the irradiation.

It is noteworthy that, except for the temporary nausea accompanying roentgen irradiation, the development of a severe gastritis in this group of patients was not manifested clinically by symptoms.

#### CONCLUSIONS

1. Moderate roentgen irradiation of the fundus and body of the stomach in man produces an acute transitory inflammation of the gastric wall.
2. The irradiation gastritis is characterized gastroscopically by hyperemia, hemorrhage, edema and adherent exudate, and, histologically, by degenerative changes in the epithelial cells and lymph follicles, increased cellular infiltration and relatively minor changes in the blood vessels.
3. Atrophy of the gastric mucosa often ensues; it is uniformly present in patients with prolonged post-radiation anacidity.
4. Irradiation gastritis is not accompanied by symptoms.

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## TREATMENT OF NON-SPECIFIC ULCERATIVE COLITIS FOR ONE YEAR WITH EXTRACTS OF INTESTINAL MUCOSA\*

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### INTRODUCTION

A review of the literature on non-specific ulcerative colitis and regional enteritis, and a study of the biology of these diseases has led us to entertain the hypothesis that the underlying basis is a deficiency of an intrinsic protective factor or factors normally present in the bowel mucosa. We assume that differences in the appearance of these lesions are due to structural differences in the mucosa of the regions involved, and to subsequent modifications produced by other factors (bacterial, proteolytic digestion, disturbed bowel physiology, etc.). This concept would correlate apparently unrelated data and bring into accord a mass of what now appears to be conflicting evidence. Nothing that we know about the biology of these diseases is inconsistent with it.

To test this hypothesis, oral therapy with extracts of the hog's small intestine was attempted in patients with non-specific ulcerative lesions of the ileum and colon. We<sup>1</sup> summarized previously the results of six months' treatment with intestinal extracts in a series of seven patients with non-specific ulcerative colitis and one patient with regional enteritis. When this study had been in progress for several months our attention was called to the experiments being conducted by Gill<sup>2</sup> in England. He also had concluded that non-specific ulcerative colitis was due to the lack of some factor which is produced in or by some portion of the small intestine. He treated 18 patients by feeding large amounts of either raw or desiccated small intestine of pigs and noted improvement in twelve patients. Continued treatment with intestinal substance appeared to be essential to prevent relapse. More than 20 years ago, Brown<sup>3</sup> also had suggested that ulcerative colitis may be of a deficiency nature. Impressed by the "void of etiologic specificity" he thought that the disease may be due to the absence from the intestinal mucosa of a protective substance or mechanism with bactericidal activity which normally protected against invasion of the intestinal wall by bacteria.

To date, we have treated a total of 71 patients with extracts of intestinal mucosa. While the overall response has been gratifying the nature of the

\* Aided by a grant from Wyeth Incorporated. The following have participated in this investigation: J. D. Allen, M.D., J. S. Gordon, M.D., W. J. Snape, M.D., and J. M. Waldron, M.D.

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disease permits evaluation of results only in those patients who have been under continuous observation for a minimum period of one year. Consequently, the present report is confined to the results obtained in only 27 patients, (8 men and 19 women) who have been treated for one year or more (Table 1). In addition, 2 men and 3 women with regional enteritis have been similarly treated but the study on these subjects will be discussed elsewhere.

TABLE 1  
*Total number of cases—71 (April 15, 1948)*

OBSERVATION PERIOD	NO. CASES	TREATMENT DISCONTINUED		TREATMENT CONTINUED	
		Intolerance	Other reasons	No. cases	Improved
Less than 6 months.....	30	6	11	13	-
7 to 12 months.....	14	1	2	11	9
Longer than 12 months.....	27		1	26	24

TABLE 2  
*27 patients (21 ambulatory and 6 hospitalized\* at commencement of study)*

<i>Sex and Age:</i> 8 men, age range 20 years to 57 years 19 women, age range 16 years to 48 years	
<i>Duration of symptoms:</i> Less than 1 year.....	8
1 to 3 years.....	14
More than 3 years.....	5
<i>Area involved:</i> Recto-sigmoid only.....	9
Recto-sigmoid and colon.....	15
Indeterminate.....	3
<i>Diarrhea:</i> Marked.....	13
Intermittent.....	7
None.....	3
Constipation.....	44

\* Included among the 6 hospitalized patients were 3 originally admitted for surgery but discharged after 3 to 7 weeks treatment without surgery.

A summary of pertinent data of these 27 patients is given in Table 2. All had failed to respond adequately to other forms of therapy, including treatment with various antibiotics, vitamin preparations, antispasmodics, protein hydrolysates, and special diets. In the patients with fever a course of penicillin therapy resulted in a drop in body temperature but no other effect.

Sigmoidoscopy, roentgenologic study of the bowel and laboratory examination of the stools established the diagnosis in each case and served to evaluate the results of therapy. These various procedures were carried out at regular intervals. The severity of the bowel symptoms was graded empirically as shown in Table 3. Since frequency in bowel movement is not a constant

feature of the disease, numerical qualification was limited to the nature of the stool—consistency, presence of gross blood, and presence of mucus. The use of these indices permitted better determination of the progress of the disease as judged by the symptoms and also permitted comparison between the responses of different patients.

Only a crude extract of intestinal mucosa was used on the patients comprising this study. This was similar to "precipitate A" used in the preparation of secretin,<sup>4</sup> except that it had been press-dried, and treated with alcohol and acetone. Studies on purification of the active principle are in progress but are greatly hindered by the lack of a rapid assay procedure. The daily dose initially was from 50 to 100 grams per day in divided portions; this amount represented 10 to 20 feet of intestinal mucosa. With improvement this amount was reduced to what was considered a maintenance dose. The earlier preparations

TABLE 3

INDEX	STOOL LIQUID	BLOOD PRESENT	MUCUS PRESENT
5	each B. M., every day	each B. M., every day	each B. M., every day
4	some B. M., every day	some B. M., every day	some B. M., every day
3	some B. M., some days	some B. M., some days	some B. M., some days
2	none	uncertain	uncertain
1	costive	none	none

of extract were not well tolerated but later preparations have been somewhat improved. Placebos were made up of a lactose preparation or of a powdered meat-casein-NaCl mixture with a protein and salt content equivalent to the extract. Recently we have also been treating a series of patients with non-specific ulcerative colitis with preparations of desiccated and defatted whole duodenum but the interval of study is still too brief to permit final interpretation of the results.

#### RESULTS

The results of the present study are summarized in Tables 1 and 4. Twenty-four of the twenty-seven patients exhibited varying degrees of improvement: symptomatic and sigmoidoscopic in 13, sigmoidoscopic only in 8, and symptomatic only in 3. In Figs. 1 and 2 are shown graphically the course of events and the influence of administration of the intestinal extract to 2 patients who may be considered as showing respectively excellent and fair symptomatic improvement. In both these patients the mucosa of the rectosigmoid showed very good healing. Treatment with intestinal extracts was maintained throughout the whole time except during the periods when a placebo was substituted or treatment withheld.

Decrease in the frequency of the bowel movements and disappearance of gross blood from the stool were prominent and early signs of improvement. In the few patients without marked bowel frequency cessation of bloody discharges from the rectum was the first noticeable change. Improvement was first noted after 2 to 5 weeks of treatment with intestinal extracts, occurring in general earlier in the patients with illness of less than one year's duration.

TABLE 4

Symptomatic improvement and sigmoidoscopic evidence of mucosal healing.....	13*
Sigmoidoscopic evidence only, symptoms not markedly altered.....	8*
Symptomatic improvement only; mucosa shows only some improvement.....	3
No evidence of improvement.....	3

\* Includes one patient with healed rectosigmoid mucosa but polyps present were not reduced.

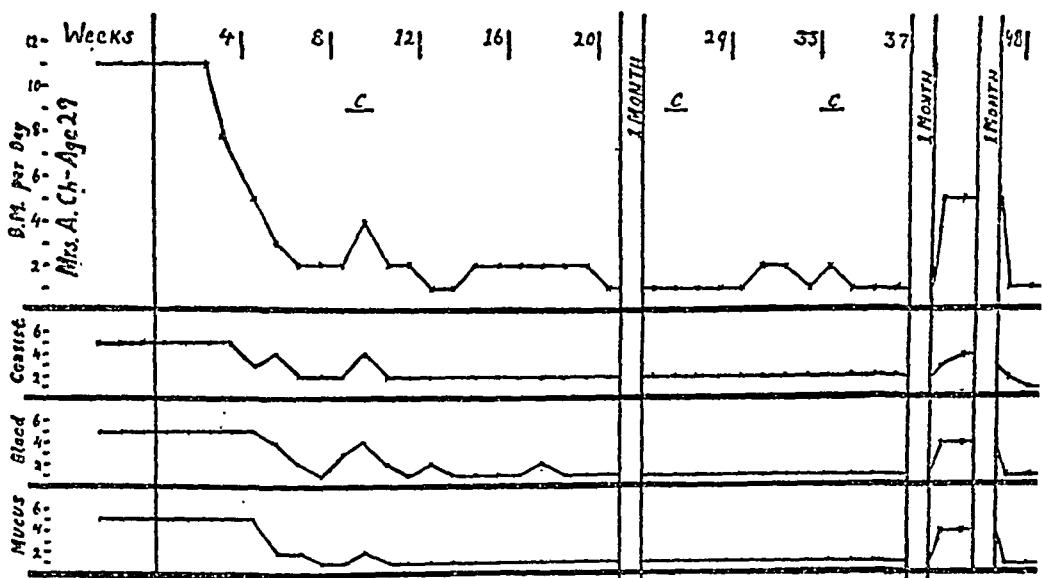


FIG. 1. Mrs. A. Ch., age 29. History of non-specific ulcerative colitis for past 3½ years. Treatment with intestinal extracts started at vertical line and maintained throughout period shown except for interval indicated by symbol "W". At "C" patient had upper respiratory tract infection.

A feature in most cases was a progressive increase in consistency of the stool. However, in 2 cases under treatment for 13 and 15 months respectively the bowel movements still remained liquid although the frequency was reduced from 8 and 10 per day to 3 and 5 per day and all gross blood had disappeared. Seven of the patients developed constipation or costiveness during the course of treatment with intestinal extract. This appeared as an extension of the process of decreasing the frequency of bowel movements which occurred in the other patients. From the patient's viewpoint the costiveness was as distressing as the previous bouts of diarrhea. It could be corrected to some extent by reducing the amount of extract taken.

Upper respiratory tract infections have long been regarded as a significant factor in the course of this disease. Most of the patients in this series experienced one or more acute colds during the year and in most of them a flare-up of symptoms resulted. However, it was our impression, based upon our observations and the patient's history, that the exacerbations were less intense than on previous occasions.

It was of interest to observe that symptomatic improvement occurred in nearly every patient before the sigmoidoscope revealed marked changes. A decrease in mucosal friability was the first change observed and was followed by

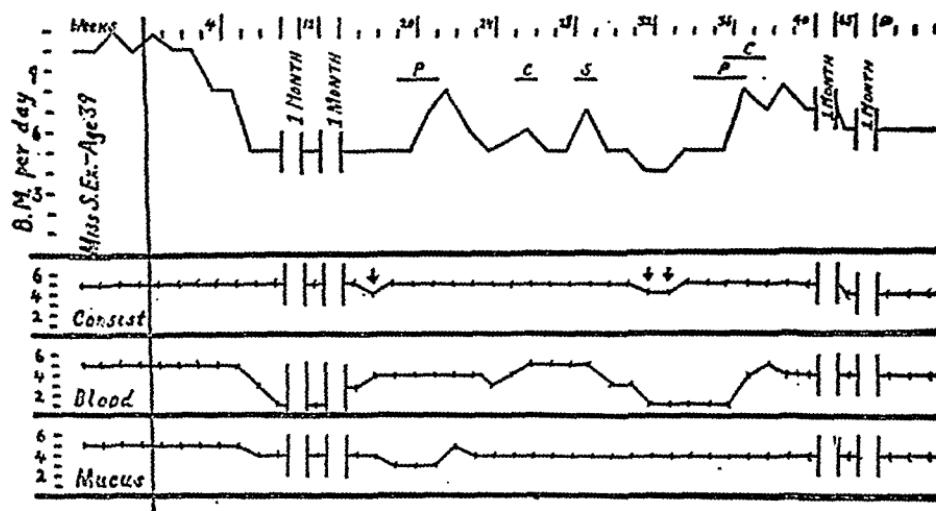


FIG. 2. Miss S. Ex., age 39. History of non-specific ulcerative colitis for past 13 years. Marked fibrotic changes in colon. Extract given throughout period. "C" indicates acute cold, "P", placebo substituted for extract. Arrows indicated formed stool, first experienced by patient in past 4 years.

gradual healing of the ulcers and disappearance of the granular changes. Direct inspection showed that improvement nearly always began at the oral end of the involved region and extended caudad. This course in mucosal improvement was in the reverse direction of the usual progress of the disease. Tenesmus was a feature in many patients as long as the lower rectal mucosa showed inflammatory change. The urge to defecate persisted even when the frequency in bowel movements had been reduced to one or two per day but disappeared when the lower rectal mucosa had healed.

X-ray changes in the colon following treatment, were dependent upon the extent of involvement of the bowel wall. Only 3 cases with widespread disease showed roentgenologic evidence of improvement. The fibrosis in severe cases is probably not reversible even though symptomatic improvement and evidence of mucosal healing were observed. In patients with the disease restricted to the rectosigmoid region the roentgenologic studies were of limited value and

served only to show that the disease was restricted and did not advance beyond the rectosigmoid during the course of treatment with intestinal extract.

Since the extracts used were prepared from the intestine of the pig, it was interesting to note the reaction in a 29 year old male patient with severe ulcerative colitis who had previously been found to be sensitive to pork and pork products. (This food idiosyncrasy was unknown to us at the time of study). Before taking the hog intestinal extract the patient was having 15 to 18 liquid bloody mucopurulent bowel movements daily. After one week of taking 30 grams of extract per day the bowel movements had increased to 45 per day, and the patient complained of severe cramps. Following a three day period during which the extract was not fed and the patient did not improve, administration of the extract was again resumed at a higher dosage level. However, the patient's condition soon became critical and he had to be hospitalized and treatment with the extract suspended. Although not proved, this would appear to be a case of sensitivity to pork similar to that found by Grossman and Ivy in a patient with peptic ulcer who also received extracts of hog intestine.

To determine the effect of the intestinal extract on normal subjects, 30 to 40 grams were taken daily by 15 healthy male volunteers (medical students) for a period of 12 to 18 days. No definite changes in bowel habits were noted. Two subjects showed a questionable tendency to become constipated and one subject had a brief episode of diarrhea which he attributed to a dietary indiscretion.

#### DISCUSSION

Two major obstacles have been encountered in the present study, namely, the absence of a method for producing experimentally in animals lesions which are similar to those seen in man, and the characteristics of the disease as it occurs in man. Experimental bowel lesions would make possible a procedure for assaying the potency of intestinal mucosa extracts and thus permit evaluation of various chemical procedures for fractionation and purification of the extracts. Unfortunately experimentally induced colon lesions are of an acute nature and heal rapidly without becoming chronic.<sup>5</sup> We are forced consequently to employ the tedious and less objective method of using patients having the disease. Non-specific ulcerative colitis and regional enteritis are chronic diseases showing periods of apparently spontaneous remissions and relapses. As with certain other chronic diseases such as peptic ulcer, rheumatoid arthritis, and psoriasis, in which there may be an associated emotional factor, in non-specific ulcerative colitis and enteritis one would expect a certain number of patients to show some response to non-specific therapies. The effects resulting from withdrawal of the therapeutic agents or substitution of a placebo were

used in this study as a measure of the therapeutic efficacy of the intestinal extracts. While the 27 patients do not constitute a large series, the remission of symptoms for long periods of time and the healing of the bowel mucosa during the year studied assisted in evaluation of results.

Roentgen examination of the colon may be of limited value as a means of determining response to treatment with intestinal extract. In one-third of the cases the disease was restricted to the rectosigmoid. The roentgen features of advanced fibrosis which include both narrowing of the lumen and decrease in length may alter greatly in the stage of remission. Bockus<sup>6</sup> believes that the changes which indicate shortening and narrowing may be the result of muscular spasm and perhaps edema of the bowel wall rather than irreversible fibrosis of all the coats of the colon. In cases of long standing, with advanced fibrosis involving the sub-mucosa and muscle coat of the colon, it is expected that the changes may be irreversible. These cases did show relief of symptoms and definite improvement in the mucosal picture, but we are doubtful that advanced fibrotic changes in the entire bowel wall can be altered.

Nearly all of the patients during treatment showed definite sustained improvement while relapses were common following either substitution of a placebo or complete withdrawal of treatment. This pattern of events is in accord with the premises on which the treatment was instituted. However, we are fully aware that the results of this study merely offer presumptive evidence, and do not constitute proof, that non-specific ulcerative bowel lesions are due to a deficiency of an intrinsic factor. The nature of the mechanisms involved in the symptomatic improvement and healing of the ulcerative areas must await further research.

The recent studies by Karl Meyer and his group,<sup>7</sup> showing increase in lysozyme content of the colonic mucus in patients with ulcerative colitis, raised the question whether the beneficial effects obtained in our patients may have been due to depression of lysozyme activity by an inhibitor in the intestinal extracts. Preliminary experiments in cooperation with Dr. Smolenz of the Wyeth Institute have shown no inhibition of lysozyme; on the contrary several preparations were found to contain lysozyme.

The decrease in frequency of bowel movements and the increase in stool consistency suggest that at least two processes may be affected—namely, the motility of the bowel and water resorption. The decrease in number of bowel movements per day, leading ultimately in some patients to a state of constiveness, probably denotes decrease in motor activity of the bowel, or a decrease in "bowel irritability". The increase in the consistency of the feces may be attributed either directly to increased absorptive activity of the colon epithelium, or indirectly to increase in fluid absorption incidental to retention of feces by the decreased motor activity of the bowel. The constipation that developed

in 7 patients may have been a return of bowel habits to what was "normal" for these patients before the onset of the disease. This is suggested by the fact that many patients with non-specific ulcerative colitis gave a history of constipation having preceded the diarrheal phase of the disease. It is also possible, however, that the constipation was an indication of overdosage, in the nature of a "rebound" phenomenon similar to that seen in overdosage with other medications. Favoring the overdosage explanation for the costiveness is the fact that it could be corrected to some extent by reducing the amount of extract taken.

It has been found repeatedly that in ulcerative colitis and enteritis the intestinal absorption of amino acids, carotene, vitamin D and other substances is greatly reduced. The degree of malabsorption is in proportion to the extent of bowel involved and to the duration and intensity of the disease. One would expect oral therapy to be more efficacious in patients with ulcerative colitis showing only mild symptoms of short duration. This may account for the better and more prompt results in the patients in our series whose illness was of less than one year's duration.

The concept that non-specific ulcerative colitis is due to the deficiency of a factor normally present in the intestinal mucosa does not imply that a complete cure is a necessary sequel of replacement of this factor. In pernicious anemia there is present always a complete anacidity but control of the anemia by administration of hog's pyloric extracts or stomach substance does not restore the capacity of the gastric parietal cells to elaborate HCl.

#### SUMMARY

It is suggested that non-specific ulcerative lesions of the bowel may be due to the absence of an intrinsic factor normally associated with the intestinal mucosa.

To date 27 patients have been treated with intestinal extracts for a period of one year or longer. All had proved refractory to other therapies and during this study received no special medications.

Distinct evidences of sustained improvement have been shown by 24 of the 27 patients after 2 to 5 weeks of treatment. In patients with frequent bowel movements the first sign of improvement was reduction in frequency, followed by disappearance of blood and decrease of mucus from the stool, and finally a return of stool consistency towards normal. The rectosigmoid showed decrease in friability, gradual healing of the ulcers, disappearance of edema, absence of mucus, and a return of the normal colon and elasticity of the mucosa. These mucosal changes in most cases commenced in the sigmoid region and were noted only several weeks after symptomatic improvement was evident. Fibrotic changes noted roentgenologically were not reversed by the treatment.

Patients less severely affected responded more promptly. Dosage requirements were adjusted for each patient. Relapses during treatment were infrequent, of short duration, and usually in connection with upper respiratory tract infections. After a successful course of therapy, withdrawal of treatment or substitution of a placebo, or use of intestinal extracts prepared by a different method resulted in a relapse with remission recurring on resumption of treatment with an effective extract.

Only certain preparations of intestinal mucosa were found effective. The only test for potency now available is the effect of the extract on the patient. The absence of a reliable animal assay procedure hinders greatly attempts to isolate the substance from the intestinal extracts.

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## ORAL TREATMENT OF CHRONIC DUODENAL AND JEJUNAL ULCERS WITH AN EXTRACT OF PREGNANT MARE'S URINE

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### INTRODUCTION

The following report represents the results obtained in the first twenty months of use of an oral given extract of pregnant mare's urine in the treatment of chronic intractable duodenal and jejunal ulcers. The patients selected for treatment had symptoms of chronic peptic ulcer for from three to twenty-nine years and had frequent recurrences during this period. Failure to respond to intensive conventional ulcer therapy over an adequate period of time, with the demonstration of a persistent ulcer crater by roentgenogram, were the prerequisites for inclusion in this clinical study. In other words, "medical failure" on intensive conventional treatment, formed the basis of selection of patients.

The results to date have been encouraging and warrant a preliminary report at this time.

### REVIEW OF THE LITERATURE

A review of the literature on enterogastrone, anthelone and urogastrone was made by Sandweiss<sup>1</sup> in November 1945, and a further comment made by Necheles<sup>2</sup>. To define these various substances, we quote from Sandweiss' review as follows: "Enterogastrone, therefore, is a humoral agent and has been defined as a chalone (inhibitor), derived from the intestinal mucosa which inhibits the motor and secretory activity of the stomach. . . . The term urogastrone may be defined as a gastric-secretory depressant which is extracted from the urine of humans. It has been shown that it occurs in male, female, pregnant and non-pregnant urine and the urine of patients with peptic ulcers seems to contain less urogastrone." In 1943, Sandweiss<sup>3</sup> named an anti-ulcer factor anthelone and defined it as "an anti-ulcer factor having a prophylactic, therapeutic and immunizing effect against Mann-Williamson ulcers without depressing gastric secretion." In June 1946, Sandweiss<sup>4</sup> again discussed anti-ulcer (anthelone) products in the treatment of peptic ulcer, and reviewed a group of articles published in the Swiss medical journals about three "new" products by a Swiss pharmaceutical firm for the treatment of peptic ulcer. Ivy<sup>5</sup> and his associates recently reported on parenterally administered enterogastrone in the prophylaxis and recurrences of experimental and clinical peptic ulcer.

Insofar as the authors are aware, after extensive literature survey, there are no reports of any extract of pregnant mare's urine being used in the treatment of chronic duodenal and jejunal ulcers.

#### MATERIAL AND ASSAY

The idea of using an extract of pregnant mare's urine in gastrointestinal ulcerations was originated by one of us (R. C. P.).

Freshly collected mid-term pregnant mare's urine is acidified and filtered. An acetone solution of benzoic acid is added to the filtrate and the resultant precipitate is obtained. The precipitate is washed and dried several times and made up into capsules with inert diluent. Each capsule contains about twenty milligrams of extract, which represents derivative from 250 cc. of urine.\*

The extract of pregnant mare's urine has a gastric secretory inhibitory effect on rats and this has been the basis of a biologic assay of the material. The technique of Friedman and Sandweiss<sup>6</sup> has been modified and assays of our material on rats show 28% to 53% inhibition of gastric secretion in doses of from 0.055 mg. to 0.110 mg. of crude extract given intravenously, as compared to the control group. Using extract purified by precipitation with aniline-alcohol, inhibition of 29% to 47% was obtained in doses of 0.0032 mg. to 0.0125 mg.

No evidence of inhibition of secretion was obtained in preliminary studies in human subjects using oral administration.

#### ANIMAL AND HUMAN TOXICITY STUDIES

Chronic toxicity studies were made on rats using a dose of extract PMU of 25 mg. six times weekly, given by stomach tube, for a total of twenty weeks<sup>8</sup>. Growth curves and frequent blood counts on both study and control groups were not significantly different. Every two weeks animals from both study and control groups were sacrificed for histologic study. The following organs were weighed and studied histologically—liver, kidney, stomach, spleen, heart, adrenal gland, ovary and pituitary. There was no significant difference in the weight of any of these organs in the study of control groups. Histologic study of the above-named organs, plus bone marrow studies, has not revealed any evidence of abnormal change.

Chronic toxicity studies by Bercovitz<sup>9</sup> in fifteen humans have been done with large doses (8 to 16 capsules daily) of extract PMU with weekly studies of the blood (red and white blood cell counts, differential blood counts, hemoglobin determinations, and sedimentation rates), complete urinalyses, including microscopic study of centrifuged specimen, and liver function studies. These studies were carried on over a period of six months. In no instance was there any evidence of abnormality noted during the period of study.

The twenty-six patients reported in this study were observed during and after the period of administration of extract PMU for evidence of drug toxicity, idiosyncrasy or intolerance and none was evident.

\* The extract of pregnant mare's urine was prepared for us by Ben-Venue Laboratories, Bedford, Ohio, and Parke, Davis & Co., Detroit, Michigan.

### SELECTION OF PATIENTS AND METHODS OF STUDY

The following criteria have been adhered to throughout this study, namely, only those patients have been included in whom the symptoms of peptic ulcer have been chronic and in whom there was roentgenologic evidence of an ulcer crater. The selection of patients was made on the basis of a long history (3 to 29 years duration) of peptic ulcer with frequent recurrences that have become increasingly resistant to conventional treatment—the so-called 'intractable ulcer' that brings the question of 'should the patient have more medical treatment or is surgery indicated?' On this basis, 220 patients with peptic ulcer were screened with the result that 26 (11.8%) were selected for study. Those patients who had high grade pyloric obstruction were excluded, as well as others who had definite surgical complications.

In all instances, when it was determined to place the patient upon therapy with extract of pregnant mare's urine, all other forms of therapy were discontinued, such as special diet, antacids, sedatives and antispasmodics. However, intermeal feedings were not forbidden during the first few weeks of PMU therapy if necessary, although they were not encouraged to follow any set routine of frequent feedings. Patients were encouraged to resume a normal schedule of three meals a day. At the time when the new therapy was instituted we were careful not to say anything that would tend to unduly encourage a favorable psychosomatic response to the new medication.

Patients were given the extract of pregnant mare's urine in capsules by mouth. The average dose was two capsules four times daily, one-half hour before meals and at bedtime. In the study some of the patients were given placebo capsules in order to have a control period for comparison.

### RESULTS OF TREATMENT

For the purpose of classification of results and simplicity of interpretation the patients were divided into three groups; the intractable chronic duodenal ulcers, chronic perforating duodenal ulcers and chronic jejunal ulcers.

GROUP I. This group consisted of sixteen patients with chronic duodenal ulcers with intractable symptoms. The average period of conventional ulcer therapy extended over a period of fifteen weeks. Because of failure with this therapy, as manifest by persistence of symptoms and presence of ulcer crater, these patients were put on a program of oral therapy with extract PMU.

One patient in this group (Case XVI) failed to improve and was considered a failure. The fifteen patients who responded favorably not only became symptom-free in an average time of four to six weeks, but also showed roentgen evidence of disappearance of ulcer crater. One patient (Case IX) responded both clinically and roentgenologically but took extract PMU for only six weeks

and discontinued the therapy against advice. He remained asymptomatic for two months then had a recurrence of symptoms.

GROUP II. This group comprised three patients with chronic perforating duodenal ulcers. One patient (Case IV) had severe penetrating type pain that failed to respond to bed rest and Sippy regimen over a period of two months. Roentgenograms showed a duodenal ulcer with a large crater. Within three weeks after he was put on a program of extract PMU he was much improved and the crater was much smaller. After a period of six weeks he was symptom-free and there was no evidence of ulcer crater. Therapy with extract PMU was continued for an additional nine months then discontinued. He

TABLE 1

	NO. CASES	SYMPTOMS DURING TREATMENT			ULCER CRATER	
		Same	Worse	Improved	Unchanged	Disap-peared
<i>Group I</i> Chronic duodenal ulcer— intractable	16	1 (6.7%)	0	15 (93.3%)	1 (6.7%)	15 (93.3%)
<i>Group II</i> Chronic duodenal ulcer— intractable perforating type	3	0	2 Operation: Chronic per-forating duo-den-al ulcer into head of pancreas in both.	1	2	1
<i>Group III</i> Jejunal ulcers	7	0	0	7	0	7
Total.....	26	1 3.8%	2 7.6%	23 88.4%	3 11.5%	23 88.5%

remained asymptomatic during the course of therapy and for three months after its discontinuance to the time of this report.

Another patient in this group (Case XII) had an eighteen year history of duodenal ulcer with frequent relapses and severe penetrating type pain for the past year. Surgery was advised but refused. Present ulcer episode failed to respond to intensive conventional therapy so he was put on extract PMU. He was pain free in eleven days and ulcer crater disappeared in five weeks. Therapy was continued and relapse occurred in two months with reappearance of duodenal ulcer with crater. Operation was performed and revealed a chronic perforating duodenal ulcer into the head of the pancreas. The third patient

in this group (Case XXI) who failed to respond to extract PMU was operated upon and a chronic perforating duodenal ulcer into the head of the pancreas with chronic pancreatitis was found.

GROUP III. This group consisted of seven patients with chronic jejunal ulcer. The average duration of conventional ulcer therapy was fourteen weeks before they were put on a trial of extract PMU. All of this group responded favorably and the average time for complete remission of symptoms was three to four weeks, and the ulcer crater disappeared by roentgenogram in from three to eleven weeks. One patient (Case XIV) was uncooperative in that when she felt better she immediately discontinued the capsules and had three recurrences of her jejunal ulcer which on each occasion readily responded to extract PMU therapy.

#### DISCUSSION

Insofar as was possible, we have set up a practical clinical study for the evaluation of treatment of intractable duodenal and jejunal ulcers with an extract of pregnant mare's urine. We are well aware of the many pitfalls awaiting an evaluation of the use of any new substance in the treatment of peptic ulcer.

It is generally accepted by gastroenterologists that with conventional ulcer therapy the average patient with uncomplicated peptic ulcer will become asymptomatic and the ulcer crater will disappear in from one to three months. There is, however, a small group of ulcer patients who do not respond to conventional therapy and constitute the group generally known as "intractable". This group in general is made up of those patients who do not do well in the hands of the general practitioner and are referred to the gastroenterologist, often with the request that surgery be considered. This group of patients with intractable ulcers, therefore, constitutes a difficult medical problem and in our opinion can well serve as the proving ground for any new type of ulcer therapy.

The main difficulty in evaluating response to therapy in humans with peptic ulcer is the absence of any measurable signs or symptoms other than the ulcer crater as visualized by the roentgenologist. The disappearance of the ulcer crater and relief of symptoms in a reasonable length of time can generally be considered evidence of favorable response.

The twenty-six patients used in this study of oral therapy with extract PMU represent failure on conventional ulcer therapy and, therefore, constitute a challenge to the test of any new type of therapy. The favorable symptomatic response, linked with the disappearance of ulcer craters within a reasonably short period of time, suggests a favorable therapeutic response.

This report represents only the clinical results obtained over a period of twenty months. In such a chronic disease as peptic ulcer, the results obtained

with a new method of therapy must await the test of time for full evaluation. It is our plan to make subsequent reports on these and other patients under study so that in time clinical reports extending over a period of years will be available.

#### SUMMARY AND CONCLUSIONS

The results of a twenty-month clinical study of a new substance, an extract of pregnant mare's urine (extract PMU) suitable for oral administration, on chronic intractable duodenal and jejunal ulcers are presented.

Twenty-six patients (11.8%) with chronic duodenal or jejunal ulcers who failed to respond to intensive conventional ulcer therapy were selected for this special study from a total of two hundred and twenty patients with peptic ulcer.

There were sixteen patients with chronic intractable duodenal ulcer in the group. All were failures with conventional ulcer therapy which had been followed for an average of fifteen weeks. They were then put on extract PMU orally. Fifteen of them improved clinically and roentgenologically. One failed to improve while on the oral extract PMU. One patient who had a good response while on the therapy, but who discontinued therapy against advice, had a recurrence of ulcer symptoms in two months.

There were seven patients in the group with chronic jejunal ulcer. All of these patients responded favorably and became asymptomatic within three to four weeks and subsequently the ulcer crater disappeared roentgenologically.

Three patients had chronic perforating duodenal ulcer. One responded favorably and the other two continued to have symptoms necessitating an operation which revealed a chronic perforating ulcer into the head of the pancreas with chronic pancreatitis.

This clinical report of a new type of therapy for chronic intractable duodenal and jejunal ulcers, resistant to conventional therapy, is encouraging and warrants continuing the evaluation of such treatment.

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## DEVELOPMENT AND EVALUATION OF GASTROSCOPY\*

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In his address, "On medical education," in 1870, Thomas Henry Huxley<sup>1</sup> said: ". . . the rung of a ladder was never meant to rest upon, but only to hold a man's foot long enough to enable him to put the other somewhat higher." This thought might well be applied to the field of gastroscopy. In the past, gastroscopists have found that the passage up the ladder of knowledge is often accomplished with difficulty and hardship. It is important that, having made progress, we do not become complacent and rest upon the present rung.

The history of gastroscopy is truly a fascinating one. Man has always been endowed with a curiosity concerning the workings of internal organs and a desire to visualize their activities directly. This has been especially true of the stomach, which frequently is man's pride and joy. Kussmaul<sup>2</sup>, in 1868, is credited with having made the first effort to accomplish direct visualization of the stomach, but his efforts proved fruitless. Subsequently, many investigators attempted the feat with varying degrees of success. Many bizarre and unusual instruments were developed in this endeavor. Schindler<sup>3</sup>, in his textbook on gastroscopy, has admirably described the vicissitudes encountered by these early investigators. Probably the greatest obstacle to the early development of a safe and satisfactory gastroscope was the discovery by von Röntgen of the roentgen rays, which proved such an extremely valuable aid in the diagnosis of gastric disease that the use of gastroscopy was abandoned temporarily.

There were physicians, however, who believed that the development of a satisfactory gastroscope offered great possibilities for a better understanding of the stomach. Fortunately, some of these physicians were endowed with a determination of purpose and a thirst for knowledge that constantly urged them to surmount apparently impossible obstacles to accomplish their purpose. These efforts finally culminated in the successful development of the flexible gastroscope by Schindler and Wolf.

The introduction of the flexible gastroscope as a diagnostic aid in the study of the interior of the stomach was greeted with considerable enthusiasm. My former associate, Dr. Vinson, and I had employed the old rigid gastroscope for many years, and although we occasionally were able to obtain an excellent view of a gastric lesion, on the whole we were not very favorably impressed with this instrument. More frequently than not, the portion of the stomach which we wished to examine could not be adequately visualized. Owing to the

\* Presidential address to the American Gastroscopic Society, Atlantic City, New Jersey, May 1, 1948.

rigid nature of the instrument, it was difficult to pass into the stomach and the esophagus was likely to be injured. We did realize, however, that an adequate flexible gastroscope might be of considerable value.

When we heard of the development of the flexible gastroscope in 1932, we became very much interested in its possibilities. Some time later, I learned that Dr. Benedict, of Boston, was in possession of such an instrument. I went to Boston to investigate its possibilities, and what I saw was indeed encouraging. I recall very well that on my return to Rochester I discussed the instrument with Dr. W. J. Mayo and Dr. H. S. Plummer. I was greatly disappointed when they expressed some skepticism as to the possible value of gastroscopy in the diagnosis of gastric disease. Dr. Mayo, however, in his usual understanding manner, encouraged me to investigate the possibilities of this procedure thoroughly, with the admonishment not to be misled by false claims. I was told to obtain a flexible gastroscope if I thought that it would be of value and could be used safely. At that time, I was unaware that Dr. Mayo and Dr. Plummer had used the rigid gastroscope about twenty-five years previously, and that the results of their experience with this instrument had been discouraging.

In 1934, Dr. Schindler came to this country to make his home. His demonstrations, lectures and writings pertaining to gastroscopy kindled a tremendous interest in the subject. The development of any new technical procedure, instrument or device that seems to offer a short cut in diagnosis is bound to attract its share of indiscriminate observers. Gastroscopy was no exception to this rule. Some of the early enthusiasts of gastroscopy, through unjustified claims and loose thinking, did the procedure more harm than good and cast the cold eye of suspicion and dislike of some of our medical colleagues upon our heads.

It might have been well if the American Gastroenterological Association had taken a hand in the development of gastroscopy as a diagnostic procedure, but such was not the case. It, therefore, remained for those of you who had faith in gastroscopy eventually to cloak it with the robe of respectability. Buie<sup>4</sup> has very aptly said, "It is through discussion that experience is analyzed and eventually, we hope, correctly interpreted, because often the correct interpretation is considerably delayed while men in a free society experiment and discuss. This freedom to try and to think and to express is our greatest strength and greatest blessing."

Realizing that it would be of value to have a means available to permit an exchange of experiences and ideas between physicians interested in gastroscopy, to assist and guide those embarking on its study, and to discourage unethical exploitation, the American Gastroscopic Club was organized. This club was the forerunner of our present organization. It was due to the cooperation of

the members of this club, and especially to the unstinting efforts and wise guidance of my predecessors in office, that gastroscopy finally reached the age of discretion.

It has been established without question that gastroscopy is a valuable aid in the study of gastric disease, but has it reached the stage at which it can or should be regarded as a distinct specialty? It is true that modern specialization has often been initiated by the discovery or development of some special instrument. Specialization is by no means a new or modern development in medicine. It was widely practiced in ancient Egypt and was also fashionable somewhat later in Greece and Rome. During the Middle Ages it all but disappeared and remained dormant until the latter quarter of the past century. Ideally, the acme of perfection would envision every physician as being able to utilize every diagnostic and therapeutic procedure in a faultless manner. While this might possibly have been conceivable seventy-five or a hundred years ago, such is not the case today. During the past century or even during the past twenty-five years, the progress that has taken place in medicine and surgery has been so great that it is no longer possible for a physician to be thoroughly familiar with all fields. It has indeed become apparent that, as Dr. William Worrall Mayo said more than fifty years ago, "No man is big enough to be independent of others."<sup>5</sup>

This dependence on others for help in the care of the sick has been the catalyzing agent that has led to the development of specialization. The American Medical Association took cognizance of such necessity as early as June, 1874, when it passed the first resolution favoring specialization. Even specialists were soon aware of dependence upon each other for help and information, and soon there evolved the formation of special medical organizations.

Actually, what does the term specialization mean? According to the Oxford Dictionary, a specialist is one who devotes himself to a single branch of a profession or subject. The advantages of such specialization have been very well summarized by Barker<sup>6</sup> in the following manner: "The increasing development of specialism in medicine is the logical continuation of the great process of division of labor with concentration upon restricted tasks that has characterized social and economic organizations in general as civilization has advanced. The differentiation of tasks keeps pace with the growing complexity of society to the great advantage both of single workers and of society as a whole. For in the first place, specialization increases productivity. When tasks are subdivided, the division results in operations that are easier of performance than those of undivided work; moreover, work is made easier by frequent repetition. Thus specialization in medicine and surgery as in commerce and industry is a device that has greatly increased the total results of professional labor."

There is no doubt that intensive study and repetition of technics should

facilitate the use of such technics and increase one's knowledge of a subject. Care must be exercised, however, to forestall a situation to which a quotation ascribed to the late Dr. Nicholas Murray Butler becomes applicable: "A specialist is one who learns more and more about less and less." That there are certain inherent dangers in specialization is recognized by the medical profession. Some of the shortcomings have been ably described by Bishop Spalding<sup>7</sup> in an excellent essay on professional education. He summarized the dangers in the following terse statement: "Division of labor makes everything cheap—man first of all; and the increasing tendency to specialization may have the effect, not only to lower the standard of professional life, but to interfere with the development in the professions of strong, many sided personalities, interesting in themselves, and lending dignity to their callings; who while they are masters in their several departments, are none the less at home in the whole world of human interests and speculation." Osler,<sup>8</sup> while recognizing the importance of specialization, warned that "the most dangerous members of the medical profession were those who were born into it, so to speak, as specialists." To avoid this danger, he advised that fundamental training in one of the basic sciences be undertaken before embarking upon a limitation to a special field.

The American Gastroscopic Society in its comparatively short span of existence has experienced the trials and tribulations inherent with growth. It has finally reached the age of maturity and its associated problems. One of the most important of these problems is that of specialization. It is advisable and proper at this time that we stop and consider the past, analyze the present and indulge in the pleasure of speculating about the future of gastroscopy, before attempting to cope with the problem.

The past history of gastroscopy is well known to most of you. Many of our errors were the result of overenthusiasm and some of our disappointments were of our own making. Gastroscopy was fortunate from its inception in having the encouragement, counsel and advice of outstanding gastroenterologists, gastric surgeons and roentgenologists. Like the developing child, we did not always heed the advice given us. We have managed, however, to survive and reach the age of maturity.

Having reached this age, we should guard against any tendency to become self-satisfied. We should retain the resiliency of youth and should continue to search for knowledge. We should be alert to initiate new advances which will alleviate illness.

In addition to determining the advisability or inadvisability of regarding gastroscopy as a distinct specialty, there is the problem of its relationship to medicine as a whole and to gastroenterology in particular. Plans must be formulated and provisions made for the adequate teaching of gastroscopy and for improvements in our present technic. What shall be the eventual require-

ments for membership in the American Gastroscopic Society? Shall we always remain independent or shall we eventually seek affiliation with the American Gastroenterological Association?

It would indeed be extremely hazardous and improper for me to try to anticipate the proper solution. There are, however, a few general principles that that, if followed, should safeguard gastroscopy. It is essential that we never neglect the patient as an individual in our enthusiasm to scan the interior of his stomach. All organizations stipulate certain requirements for membership. This is often advisable and essential but the real purpose of the society, that is, the advancement of knowledge and acquirement of information, frequently is lost. It is to be hoped that we may avoid these pitfalls. Dr. Palmer<sup>9</sup> discussed the question of membership in his presidential address before the American Gastroenterological Association and said what that organization regarded as essential for its proper development. He said: "The view finally prevailed that the specialist in digestive disease should be primarily an internist and secondarily a gastroenterologist. In the past and at present, some of our distinguished members have been and are physiologists, pathologists, surgeons, radiologists and psychiatrists. The Society has usually taken the stand that its formation is to promote the study and knowledge of the digestive tract, bringing together workers of various background."

The future of gastroscopy is something that no man can foretell. The vista presenting itself is, however, a very inviting one. Much progress is to be anticipated in gastroscopic diagnosis owing to improvements in instruments and gastroscopic technic. In the not-too-distant future, it will undoubtedly be possible to distinguish benign lesions from malignant lesions with greater certainty than it has been in the past. The entire field of functional disturbances involving the gastric mucosa presents an alluring problem. There is also the prospect of possibly prognosticating the future course of a certain type of gastric mucosa on the basis of its general appearance and functional capabilities.

It behooves us not to become complacent. It seems to me that it would be wise and advisable for this society, for its future and successful survival, to establish a close liaison with the American Gastroenterological Association, if not to become affiliated with it, at least to endeavor to arrange a joint yearly program. Such a program would indeed prove of great benefit to us. Should we, on the other hand, limit ourselves to the small restricted field of gastroscopy, then I fear that, like the grape on the vine without sunlight and nourishment, we shall dry up and die.

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## INVOLVEMENT OF THE STOMACH IN MALIGNANT LYMPHOMA

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### INTRODUCTION

Since the report by Hodgkins in 1832<sup>1</sup>, of the syndrome characterized by enlargement of the lymph glands, pathologists and clinicians have been unsuccessful in standardizing the terminology or classification of this condition. Wunderlich<sup>2</sup> in 1858 used the term malignant lymphoma to describe the enlarged lymph glands. As early as 1835 Briquet<sup>3</sup> described aleukemia of the digestive tract and in 1865 Cohnheim<sup>4</sup> called this condition "pseudoleukemia". Kundrat in 1893<sup>5</sup> separated a single syndrome which he called lymphosarcoma. In order to clarify this chaotic condition, Minot and Isaacs<sup>6</sup> suggested the term "lymphoblastoma" which would include the principal neoplastic manifestations of lymphatic leukemia, aleukemia (pseudoleukemia), lymphogranulomatosis (Hodgkins disease), and lymphosarcoma. This term still does not satisfy the clinician, as it leaves out the myeloid leukemias, the myelomas, and plasma cell tumors. The term malignant lymphoma enables the clinician to group together all cases of hematopoietic malignant neoplasms and separate them from true malignancies. This term has been used at the University Hospital for the past twenty years or more. The pathologist having an opportunity to study the histology of the hematopoietic neoplasms classifies them according to cell type. They, too, cannot agree on a standardized classification as any classification will depend on the phase of the disease at time of biopsy and the part of tissue section examined. Table 1 outlines the classification of the hematopoietic malignant neoplasms used by the Department of Pathology at the University of Iowa.

Although involvement of the gastrointestinal tract by malignant lymphoma has been described many times, it is diagnosed very infrequently during life.

### OBSERVATIONS

In a survey of 12,936 autopsies performed by the Department of Pathology of the University of Minnesota, only seventy-seven cases of leukemia were found, fifty-five of the lymphatic type and twenty-two of the myelogenous type<sup>7</sup>. Two of the lymphatic leukemia cases showed local gastrointestinal nodular and ulcerative lesions, while only one of the myelogenous group showed thickening of the walls of the gastrointestinal tract without nodule or ulcer formation. In another review of 16,254 autopsies at the University of Minnesota, Hodgkins disease of the gastrointestinal tract was found in only three instances, while seven cases of lymphosarcoma were discovered.<sup>7</sup> In eighty

cases of Hodgkins disease treated by the roentgentherapy department of the University of Minnesota Hospital, only one case proved to have involvement of the digestive tract.<sup>7</sup> The incidence of malignant lymphoma of the digestive tract as noted above appeared to be lower than expected when compared with

TABLE 1  
*Classification of hematopoietic malignant neoplasms*

I.	Mycloid
a.	Leukemia
b.	Myelomas (multiple myeloma; plasma cell)
II.	Lymphoid
a.	Leukemia
b.	Non-circulating lymphoma
1.	Lymphoid cell type { blastic—lymphosarcoma cytic
2.	Giant follicle
3.	Hodgkins
4.	Reticulum cell sarcoma
5.	Aleukemic leukemia

TABLE 2  
*Postmortem material—1941 thru 1946*  
Total number of autopsies—1767

Number of malignant lymphomas	
Lymphocytic leukemia.....	15
Myelogenous leukemia.....	9
Monocytic leukemia.....	1
Hodgkin's disease.....	10
Total.....	35
Number showing gross and/or microscopic evidence of involvement of stomach	
Lymphocytic leukemia	
Acute.....	1
Chronic.....	6
Myeloid leukemia	
Acute.....	1
Chronic.....	4
Hodgkin's disease.....	3
Table.....	15

our own experience. From 1941 to 1947, the Department of Pathology at the University of Iowa performed 1,767 autopsies. Thirty-five cases of malignant lymphoma were found, ten of which were Hodgkins disease and twenty-five were leukemias. Of the thirty-five cases, fifteen showed either gross and/or microscopic evidence of involvement of the stomach (see Table 2).

Patients with malignant lymphoma usually return to the hospital at frequent intervals for observation and treatment. Despite the fact that many such patients are treated in this hospital, only a few of these cases remain until death. Also, during the years 1941 to 1947, we experienced a shortage of materials making it necessary to re-use microscopic slides. For these reasons we have been unable to correlate the clinical findings of our cases with pathologic material.

The gross pathological picture can vary from slight thickening of the mucosa to a mass large enough to cause obstruction.<sup>9</sup> In the leukemias, one often finds small areas of infiltration and thickening of the mucosa. In the area of thickening, the mucosa may be denuded resulting in ulceration and hemorrhage. At times only small petechial hemorrhages can be found. The mucosa can be raised and frequently forms exaggerations of the rugae not unlike the "convolution of the brain". This occurs more often in chronic lymphatic leukemia than in the other types of leukemia and when present is usually located near the pylorus. Grossly the pathologic picture of Hodgkins disease may vary from small thickened areas of the mucosa to large, infiltrative, ulcerating lesions which may result in obstruction or perforation. Microscopically these neoplasms reveal invasion of the mucosa and submucosa only. The characteristic cell type infiltrates into the mucosa or submucosa, either as small islands of cells or as discrete nodules, causing the mucosa to be projected into the lumen. The cells are packed closely together, producing edema of the submucosa, and by pushing outward, distort the mucosal patterns. The cellular infiltration seldom extends below the submucosa. In Hodgkins disease the microscopic picture of scarring and fibrosis is often seen in the gastric mucosa and is similar to the changes in the lymph nodes.

The fact that the histologic changes of malignant lymphoma can occur in the gastric mucosa raises the question whether or not these changes can be seen gastroscopically. Schindler in his text states that leukemic infiltration of the stomach has not been observed through the gastroscope.<sup>9</sup> In order to answer the above question, it was decided to gastroscope all the patients with malignant lymphoma seen at the University Hospital.

From 1941 to 1947, we found fifty-three patients with malignant lymphoma who gastroscopically showed characteristic changes in the stomach. As was noted above, during the same period, only fifteen instances of involvement of the gastric mucosa were found at autopsy (see Table 2). At first, due to inexperience, many instances of involvement of the gastric mucosa were probably overlooked. The type of hematopoietic neoplasm found in these patients is outlined in Table 3. One case of lymphosarcoma was omitted from this discussion as the case history and gastroscopic findings have been reported previously.<sup>10</sup> The ages varied from nineteen to seventy-five years and the sex distri-

bution was about equal. There was no correlation between type and duration of symptoms, degree of free acid, and extent of involvement. Practically all the individuals had normal roentgenologic findings. Furthermore, the gastroscopic picture was no indication of the type of hematopoietic neoplasm present.

Many of the patients showed marked distortion of the stomach as a result of an enlarged spleen, an enlarged liver, or an abdominal mass. This led us to transilluminate the abdomen in each case in order to determine whether masses or enlarged solid organs could be detected.

The most frequent gastroscopic finding in our cases was a granular mucosa seen most commonly on the anterior wall near the angulus. This is seen best in Depth II with the handle of the instrument in the nine or eight o'clock

TABLE 3  
*Gastroscopic material*

Number of patients.....	53
Number of gastroscopies.....	71
<b>Lymphatic leukemia</b>	
Acute.....	0
Chronic.....	22
Total.....	22
<b>Myelogenous leukemia</b>	
Acute.....	1
Chronic.....	9
Total.....	10
<b>Monocytic leukemia</b>	
Acute.....	0
Chronic.....	1
Total.....	1
Hodgkin's disease.....	20

positions. The next common site was the posterior wall of the antrum, and the least frequent site was in the posterior wall. The granular area usually appears as high lights in dry mucosa. At times these nodules are discrete and large enough to extend above the surface. This same appearance of small nodules in an otherwise normal mucosa has been found in the rectum and sigmoid of a few of these patients. In the bowel they are different from the granular mucosa of ulcerative colitis in that they are fewer in number and larger in appearance. The color of the gastric mucosa varied from extreme pallor to the normal orange red depending upon the degree of anemia present. In only a few instances could blood vessels be found while small areas of hemorrhage were more

common. In many of the individuals, areas of edema were noted, these having the appearance of myxomatous tissue.

The following gastroscopic report is representative of this type of involvement: R. L., male, aged 45. Gastroscopic No. 2140. Diagnosis: Myelogenous leukemia. White blood count 288,000. The instrument was passed with ease and Depth I readily visualized. Here the structures appeared normal, the mucosa was of good color and peristalsis was active. On the posterior wall of the antrum, many high lights were noted in an area about one cm. in diameter. About fifty high lights were present in this small area. It was felt that the high lights might be the result of fluid. Therefore the scope was rotated, withdrawn slightly and the omniangle switched on but at all times the "goose pimples" were always seen in the same spot. The instrument was withdrawn into Depth II. The anterior wall and greater curvature were normal. The folds on the posterior wall had the appearance of "goose pimples". These raised areas were different from hypertrophic gastritis or areolae gastricae as they were more discrete, were about one mm. in size and caused no distortion of the folds or valleys between the rugae. In Depth III a few of the folds on the posterior wall were reddish brown in color and in one area had the appearance of a gelatinous mass, raised above the surface. A few small areas of hemorrhage were present in both Depths II and III.

The second type of involvement seen in this series was the presence of a nodule usually surrounded by abnormal appearing mucosa. The small mass usually was found near the cardia and on the posterior wall more often than on the anterior wall. One patient having such a mass on the anterior wall near the cardia succumbed and at necropsy this nodule proved to be an area of infiltration due to lymphatic leukemia. The masses are small, about one cm. in diameter, usually of a darker color than the surrounding mucosa and quite often associated with considerable hemorrhage. Rarely could the origin of the bleeding be discovered.

The following gastroscopic report is typical of such a case: H. H., male, aged 50. Gastroscopic No. 822. Diagnosis: Lymphatic leukemia. White blood count 10,400. The instrument was introduced with comparative ease but just as it entered the stomach a marked resistance was encountered. Transillumination of the abdomen revealed the stomach to be under the right costal margin extending to about the right anterior axillary line. Apparently the stomach was being forced upward and anterior by a mass in the abdomen. The spleen could also be outlined and filled the left half of the abdomen. At no time could the operator orient himself as to depth. By rotating the handle to the two o'clock position the pylorus was finally visualized. The mucosa in the antral area was of a slate gray color, pale and dry. Peristalsis was observed both gastroscopically and by transillumination. No evidence of bleeding was noted in this region. The instrument was withdrawn slightly and apparently approached Depth III. The mucosa over both anterior and posterior walls still showed

the slate gray color. There was an area in the anterior wall which was raised giving the impression of marked thickening. This mass as about one and one half cm. in diameter and had a brownish color.

This patient received considerable roentgenotherapy and was re-gastroscoped twenty-six months later. At this time he still showed the peculiar slate gray colored mucosa. There was considerable bleeding throughout the entire stomach making it impossible to visualize the area on the anterior wall. We were unable to examine him again as he succumbed soon after being discharged from the hospital.

The last type of lesion we encountered was an ulceration of the gastric mucosa. This form of involvement was only seen in two cases of Hodgkins disease. In both instances the ulceration was noted in the greater curvature. The ulcer in one case appeared to be in a mount of tissue, while in the other the mucosa was not thickened. The floor of the ulceration was brownish in color, the margins were undermined and the ulcer edge was soft. In both, the lesion was oval in shape. The surrounding mucosa was normal.

The following is the gastroscopic report of one of these patients: H. W., female, aged 52. Gastroscopic No. 2025. Diagnosis: Hodgkins disease. The instrument was passed with ease and Depth I readily visualized. Nothing abnormal was noted. The scope was withdrawn into Depth II. With the handle in the seven o'clock position the greater curvature was seen. On the greater curvature, just proximal to the musculus, a round elevated mass was noted. This was less than a cm. in diameter. Just to the left of this another elevation was noted, somewhat larger in diameter, but flatter than the first nodule. The mucosa over these areas appeared normal. Between these two elevations a round ulcer about one half cm. in diameter was seen. The ulcer was deep, the base was concave being brownish in color, and the sides disappeared under the overhanging margins. The ulcerated area had the appearance of a narrow necked flask. No activity was noted in this region. The rest of the stomach appeared normal.

She was re-gastroscoped one month later following roentgentherapy. The nodules were larger in size, the ulcer opening was about the same, but looked as if it had excavated deeper in the gastric wall. No changes in the surrounding mucosa were noted. The most striking appearance of the ulcer were the soft rounded margins. Resection of the stomach was advised, but the patient refused to be operated. She succumbed a few months after discharge from the hospital.

#### SUMMARY

Hematopoietic neoplasms involve the stomach with greater frequency than the medical literature would indicate. The histologic changes are found in the submucosa and mucosa making it possible to observe them gastroscopically. When patients with malignant lymphoma are gastroscoped routinely, many are found to have infiltration of the gastric mucosa. Three types of involvement have been described, the commonest being minute nodules in the mucosa giving

Out of a group of 402 consecutive patients examined gastroscopically at the Jefferson Hospital from December 1945 to December 1947, fifty-seven had cancer of the stomach. In all the patients routine laboratory and gastrointestinal roentgen studies were performed; also in the majority a histamine fractional gastric analysis was carried out. Since most of these patients were from the medical and surgical wards, the roentgen studies were performed for the most part by residents being trained in roentgenology. The diagnosis was confirmed at operation or necropsy in all but four patients; and in these the clinical picture left little doubt as to the correctness of the diagnosis.

Of the entire group seven were found to have primary cancer and sixteen secondary involvement of the cardia (Table 1); in fifteen the lesion was located in the body and in nineteen in the pylorus.

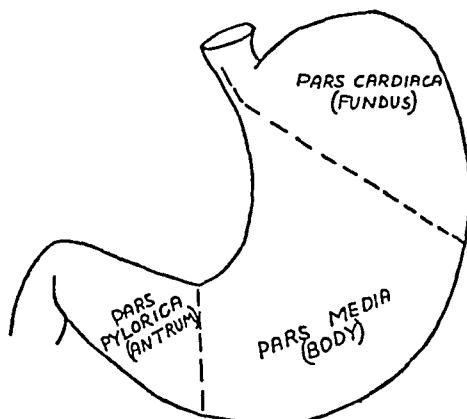


FIG. 1. ANATOMIC DIVISIONS OF THE STOMACH

If a line is drawn straight down through the esophagus to the greater curvature of the stomach the portion of the stomach to the left of the line is the pars cardiaca, or fundus.

The males predominated in this group five to one and the average age was fifty-five years. The predominant symptom when the patient was first seen was a mild to moderate dyspepsia; rarely were symptoms or signs definite enough to substantially establish the diagnosis. It was of some interest that four patients (Nos. 1, 2, 3 and 9) had had cholecystectomy for gall stones one to four years previously without relief of symptoms. Gross or occult blood was present in the stools of only thirteen patients. A blood count lower than 3.8 million r.b.c.'s and hemoglobin lower than 68 per cent was found in twenty patients, or approximately one-third of the group. Gastric analysis was performed in thirty-six patients; in thirteen, or 36 per cent, free acid was present and in twenty-three, or 64 per cent, it was absent.

A clinical diagnosis could not have been arrived at in these patients without a roentgen and gastroscopic examination. Diagnosis made on the basis of these two methods of investigation correlated well when the lesion was located in the

TABLE 1

*Twenty-three patients with neoplastic involvement of cardia of stomach*

NO.	PATIENT	GASTROSCOPY	ROENTGEN-RAY	OPERATION
1	N. C.	obstruction	large greater curvature lesion	fundus and esophagus involved
2	R. C.	obstruction	large defect distal portion	body, fundus and esophagus
3	J. H.	obstruction	middle and upper $\frac{1}{3}$ involved	body, fundus and esophagus involved
4	H. M.	obstruction	*a) negative b) malignant cardia	nitrogen mustard
5	H. S.	cancer cardia	a) lung cancer b) suspect benign ulcer; cancer not ruled out c) same as b)	not operated
6	J. R.	lesser curvature near cardia	a) no lesion; retention b) unsatisfactory c) neoplasm not ruled out	cancer cardia at necropsy
7	J. B.	cancer cardia	questionable lesion	cancer; resection through tumor tissue in fundus
8	W. W.	cancer cardia	questionable lesion	a) refused 6 Mar. '47
9	G. J.	cancer cardia	negative	b) 10 July '47, inoperable
10	J. S.	obstruction; open tube showed stenotic lesion	normal esophagus thin antrum with ulcer—probably malignant	total gastrectomy
11	J. B.	obstruction with loss of tip	negative	not operated; being followed
12	A. G.	a) negative '42 b) obstruction 1-15-47 c) open tube—pressure from without; no neoplasm visualized 1-18-47	a) defect cardia but not cancer b) defect seen again on 1-13-47	refused operation
13	F. D.	cancer upper $\frac{1}{3}$ seen	cancer lesser curvature extending to antrum	cancer cardia
14	L. D.	obstruction; open tube—negative	narrowing distal esophagus suggestive of neoplasm	extensive
15	E. D.	cancer middle and upper $\frac{1}{3}$ stomach	polypoid lesion greater portion stomach, probably malignant	total gastrectomy cancer body and fundus
16	J. O.	cancer mid and upper $\frac{1}{3}$ stomach involving cardia	negative	cancer fundus with spread to esophagus
17	J. McG.	cancer cardia and lesser curvature	cancer of antrum	cancer lesser curvature with involvement cardia
				cancer lesser curvature extending into esophagus
				refused operation

TABLE 1—Continued

NO.	PATIENT	GASTROSCOPY	ROENTGEN-RAY	OPERATION
18	M. M.	cancer body and high into cardia	cancer pylorus	whole stomach involved
19	T. M.	cancer middle and upper $\frac{1}{3}$	cancer body with involvement high in lesser curvature	cancer body and high in fundus
20	L. S.	cancer body and high in cardia	leather bottle stomach	whole stomach infiltrated
21	M. C.	cancer antrum and high lesser curvature	cancer body and cardia	extensive lesion of body
22	D. M.	cancer body probably involving cardia	diffuse scirrhous infiltration	scirrhous infiltration of whole stomach
23	S. D.	cancer greater curvature and fundus	large lesion on greater curvature involving fundus	greater curvature and cardia

\* When a), b) and c) are used they represent first, second and third examinations respectively.

lower or middle third of the stomach; the diagnoses were the same in these patients except in two instances where a lesion located just proximal to the pylorus was recognized roentgenologically but not gastroscopically and one instance where a lesion located in the body was found by gastroscopy alone. However those lesions located in the upper third of the stomach either primarily or by extension of a lesion located lower down were more frequently recognized gastroscopically.

Twenty-three patients or 40.2 per cent of the entire group showed neoplastic involvement of the upper third of the stomach. Six of these patients had a primary cancer of the cardia, five of which were diagnosed by gastroscopy but not by roentgen-ray. In one instance (Case No. 11) the roentgen study was normal and yet impassable obstruction was encountered when gastroscopy was attempted.

*Case No. 11:* J. B., white male, age fifty-six years, coal miner. Constant burning, perumbilical pain and vomiting for six weeks. Early in 1943 treated for gnawing epigastric pain with diet and antacids. November 1943 massive hematemesis. Treatment continued for about one year. Hernia repair January 1944 and was told ulcer had healed. July 1944 pain in epigastrium recurred without prolonged relief until present. Hg. 74%; r.b.c. 4.4 million; w.b.c. 6,850. Feces positive to benzidine test.

*Gastrointestinal roentgen-ray:* normal.

*Gastroscopy:* The gastroscope was passed without difficulty until the lower portion of the esophagus was reached. Here obstruction was met which could not be passed. At first this appeared to be pronounced cardiospasm but in spite of waiting and

applying gentle pressure the instrument could not be introduced into the stomach. Upon withdrawal of the instrument the rubber tip was missing. Immediate fluoroscopy showed this tip to be located high in the stomach or in the lower esophagus, and it was inferred that it was held there by a scirrhous neoplasm of the cardia.

*Esophagoscopy:* Narrowing of the lower end of the esophagus was found but the foreign body itself could not be visualized nor could the esophagoscope be passed for any distance into the stomach. Tissue secured with the aspirating tube for biopsy proved to be adenocarcinoma.

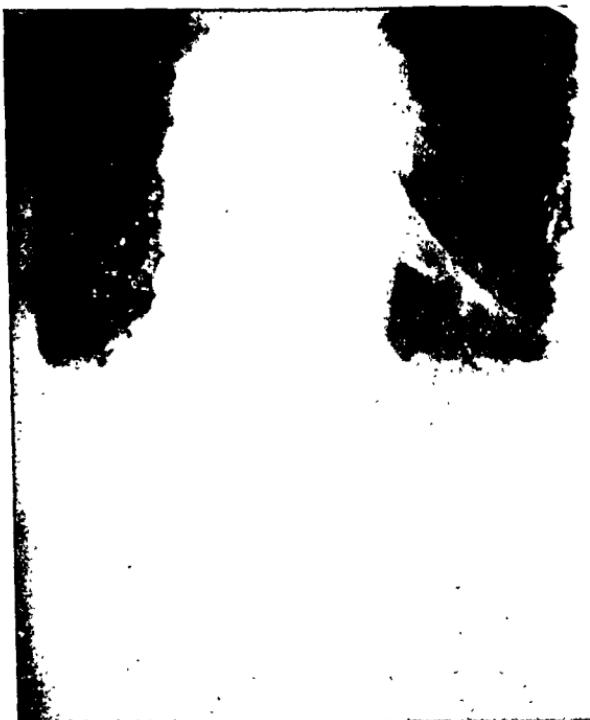


FIG. 2. ROENTGEN VIEW SHOWING DETACHED ROUND RUBBER TIP OF GASTROSCOPE FIXED IN CARDIA DUE TO CONSTRICTING SCIRRHOUS CARCINOMA (CASE 11)

The rubber tip remained fixed in the upper stomach (Fig. 2) until removed surgically five days later. A large cancer of the cardia with extensive local metastases and fixation prevented resection of the lesion. The patient recovered from the operative procedure and was discharged.

This experience was impressive because such an extensive lesion could pass unrecognized on a routine roentgen examination and emphasizes the importance of interpreting obstruction at the cardia during gastroscopy.

The following five patients (Nos. 5, 6, 7, 8 and 9) were found to have primary cancer of the cardia by gastroscopy alone (Table 2).

*Case No. 5:* H. S., white male, sixty-seven years of age, shoulder and chest pain for six months. Four years ago cholecystectomy for gall stone, but incomplete relief of pain. Since that time treated irregularly for peptic ulcer. Some loss of weight recently.

*Roentgen-ray examination:* Chest: metastatic or primary bronchogenic carcinoma of right upper lobe; gastrointestinal: suspect benign gastric ulcer or possibly primary carcinoma of lesser curvature.

*Gastroscopy:* Carcinoma of lesser curvature involving cardia and possibly lower esophagus.

Bronchial secretions were found to contain cancer cells. Because of the patient's general condition and the presence of multiple lesions operation was not undertaken. Nitrogen mustard was given for a short time. Death occurred suddenly one month later. Necropsy revealed carcinoma of the upper third of the stomach with involvement of the esophagus and metastases to the lungs.

TABLE 2  
*Primary cancer of cardia*

CASE NO.	GASTROSCOPY	ROENTGEN-RAY	OPERATION
5	cancer cardia	suspect ulcer, cancer not ruled out	cancer at necropsy involving cardia
6	cancer cardia	neoplasm not ruled out	cancer involving cardia
7	cancer cardia	questionable lesion	cancer cardia
8	cancer cardia	questionable lesion	cancer cardia
9	cancer cardia	negative	not operated

*Case No. 6:* J. R., white male, age fifty-seven years. Vomiting and epigastric pain for three months. Milk diet and alkaline powders have relieved symptoms recently. Tarry stool noticed once two weeks ago. Gastric analysis: free acid 40 units, total acid 60 units at one hour.

*Roentgen-ray examination:* the first two examinations were unsatisfactory due to food retention; on the third examination neoplasm of the stomach was not ruled out.

*Gastroscopy:* pebbled infiltrative mass involving the lesser curvature and cardia. At operation an extensive lesion involving the body and cardia with metastases to the liver was found.

*Case No. 7:* J. B., white male, age fifty-seven years, rabbi. Three months ago patient fainted at meal time for no apparent reason. A diagnosis of anemia was made and he was treated for this until the present. For past two weeks slight, intermittent epigastric pain. Hg 58.3%, r.b.c. 3.8 million, e.b.c. 4,900.

*Gastrointestinal roentgen-ray:* questionable lesion in fundus.

*Gastroscopy:* The gastroscope was passed without difficulty and a satisfactory view of the pylorus and antrum showed no abnormalities in this region. However on the anterior wall of the cardia there was a large white mass projecting into the lumen of

the stomach which was covered with clotted blood. Impression: carcinoma of the anterior wall of the cardia.

This patient refused operation for six months, during which time symptoms progressed until he was unable to swallow. Exploratory operation at this time revealed an inoperable lesion of the cardia with extensive metastasis.

*Case No. 8:* W. W., white male, age fifty-nine years, coal miner. Perfectly well until twelve weeks ago when he noticed mild epigastric burning somewhat relieved by alkalies. Noted a tarry stool on one occasion and vomited a small blood clot recently. Lost about thirty pounds in past seven weeks. Hg 78%, r.b.c. 4.8 million, w.b.c. 6,500. Stool positive to benzidine; gastric analysis showed no free hydrochloric acid.

*Gastrointestinal roentgen-ray:* four separate examinations were negative for an intragastric lesion, although prior to admission a defect, the nature of which was questionable, had been found on roentgen study.

*Gastroscopy:* A sessile mass about 2.0 cm. in diameter with an irregular craggy surface showing a number of small submucosal hemorrhages and erosions was noted on the greater curvature toward the anterior wall. This mass seemed well circumscribed and differentiated from normal mucosa noted on the lesser curvature and posterior wall. Impression: sessile, polypoid carcinoma of the cardia.

At operation a mass approximately three to four times the size of that described gastroscopically was found in the cardia. A total gastrectomy and splenectomy were performed (Fig. 3). The patient convalesced satisfactorily and is free of symptoms at present.

*Case No. 9:* G. J., white male, age seventy-two years. This patient had a cholecystectomy nine months ago for gall stone. Symptoms of abdominal discomfort were relieved for only a few months when epigastric fullness after meals recurred. There was a gradual loss of weight and a low grade jaundice slowly developed. A mass the size of an orange was palpable in the epigastrium. Hg 75%, r.b.c. 3.8 million, w.b.c. 8,000. Gastric analysis: free acid 33 units, total acid 50 units, at one hour.

*Gastrointestinal roentgen-ray:* normal.

*Gastroscopy:* The gastroscope was passed without difficulty and a satisfactory view of the pylorus and antrum was obtained. No abnormalities were noted in the lower portion of the stomach. In the cardia, however, a craggy, infiltrated tumor mass about 2.0 cm. in diameter covered with carmine red mucus was noted. The mass did not appear to involve the esophagus. Impression: carcinoma of cardia of stomach.

This patient is still under observation awaiting operation.

The next group of patients were segregated because neoplastic involvement of the cardia secondary to a lesion lower in the body was recognized by gastroscopy alone (Table 3).

There are five patients in this group (Nos. 13, 15, 16, 17 and 18). One of these patients refused operation but the progress of his disease leaves little



FIG. 3. GROSS APPEARANCE OF ADENOCARCINOMA OF CARDIA  
Total stomach removed and lesion noted at junction of esophagus and cardia (Case 8).

TABLE 3  
*Cancer of body involving cardia*

CASE NO.	GASTROSCOPY	ROENTGEN-RAY	OPERATION
13	cancer body and cardia	cancer antrum	refused operation
15	cancer body and cardia	cancer pylorus	whole stomach
16	cancer body and cardia	negative	cancer lesser curvature and esophagus
17	cancer body and cardia	cancer body	cancer lesser curvature and esophagus
18	cancer body and cardia	cancer lesser curvature and antrum	cancer fundus and esophagus

doubt as to the correctness of the diagnosis; the remaining four patients were operated upon and the diagnosis of involvement of the cardia confirmed in each. In three patients the lower esophagus was also involved. Total gastrectomy was performed in two patients (Nos. 13 and 16) and both were living six and eight months respectively following operation.

In a third group of patients the first gastrointestinal roentgen-ray examination showed a lesion in the body or distal third of the stomach or was negative while on gastroscopy obstruction at the cardia was encountered (Table 4).

There are five patients (Nos. 1, 2, 3, 4 and 11) in this group; one of which has been described, (Case No. 11). Involvement of the cardia was confirmed by operation in three; operation was refused in one, and in the fifth the progress of the disease established the diagnosis. The latter patient developed secondary involvement of the cardia following excision of a pigmented mole on the back.

TABLE 4  
*Cancer of body involving cardia causing obstruction to gastroscope*

CASE NO.	GASTROSCOPY	ROENTGEN-RAY	OPERATION
1	obstruction at cardia	large greater curvature lesion	cancer fundus and esophagus
2	obstruction at cardia	large defect distal portion	cancer body and fundus, inoperable
3	obstruction at cardia	a) negative 9 Dec. '47 b) cancer cardia 31 Dec. '47	not operated due to metastases
4	obstruction at cardia	probable malignant ulcer of antrum	refused operation
11	obstruction at cardia	negative	extensive cancer cardia

A biopsy of an axillary lymph node showed melanotic sarcoma. Investigation of the cause of epigastric pain and vomiting by roentgen-ray was first reported negative. Gastroscopic examination was then performed and impassable obstruction met. Upon repeating the roentgen study a lesion in the cardia was plainly demonstrable.

While it is obviously impossible to make a diagnosis on the basis of obstruction without seeing the lesion, it appears from these figures that a careful re-evaluation of such patients is always required before concluding that such obstruction is due to cardiospasm.

There were five patients (Nos. 19, 20, 21, 22 and 23) in whom a tumor of the body with involvement of the cardia was recognized both by gastroscopy and roentgen-ray study (Table 5).

In two patients (Nos. 3 and 14) obstruction at the lower esophagus was encountered when gastroscopy was attempted; in one a lesion of the body with

cardia involvement was noted and in the other cancer of the esophagus was suspected on roentgen study. At operation both patients were shown to have carcinoma of the cardia and lower esophagus. In a third case (No. 12) gastroscopy was reported as negative in 1942, at which time the roentgenologist observed a lesion in the cardia which he did not consider cancer. The patient gradually deteriorated and reexamination by roentgen-ray in 1947 again showed a lesion in the cardia which was suspected of being carcinoma. Gastroscopy was then attempted but obstruction of the lower esophagus was encountered. An open tube esophagascopy was negative. At necropsy carcinoma of the cardia with widespread metastases was found.

TABLE 5  
*Miscellaneous group of cancer of body, cardia, or body and cardia*

CASE NO.	GASTROSCOPY	ROENTGEN-RAY	OPERATION
3	obstruction	cancer body and cardia	body and fundus involved
12	a) negative 1942	a) defect cardia '42 but not cancer according to Roentgenologist	
	b) obstruction 1947 (open tube examination, negative)	b) defect of cardia '47, suspect cancer	necropsy, cancer fundus with metastases
14	obstruction (open tube examination negative)	suspect cancer esophagus	cancer fundus involving esophagus
19, 20, 21, 22 and 23	5 patients involving body and cardia	5 patients involving body and cardia	5 patients involving body and cardia

#### DISCUSSION

The significance of these findings becomes more apparent when considered in the light of present day surgical treatment for cancer of the stomach.<sup>4, 5, 6, 7</sup> The most efficient means of improving the outlook for this disease today is the successful employment of total gastrectomy. Pack, et al,<sup>8</sup> by this means, raised their resectability rate 2.4 per cent. They feel that the removal of the stomach and tributary lymph nodes en bloc is the ideal operation for gastric cancer and is the only technique which embodies the philosophy applied to the treatment of cancer of the breast or colon. Of the forty-one patients in whom they performed total gastrectomy, twenty-five, or 61 per cent, showed involvement of the proximal stomach. The extent of the lesion and the type of operation required in these patients could never be ascertained from the history, but was learned only by careful roentgen and gastroscopic study. The importance of recognizing the extent of a given lesion preoperatively is indicated by the experience of Longmire,<sup>9</sup> who states that the upper margin of the neoplasm in the wall of the stomach could not be determined by palpation alone at the time

of operation in 24.5 per cent of the cases. Ransom found on some occasions that proximal involvement was detected only when the stomach was transected for a proposed sub-total resection.<sup>10</sup> He feels that the three following types of carcinoma require total gastrectomy. a) Lesions which involve all or nearly all of the stomach. This group includes both the small "leather bottle" stomach due to infiltrating scirrhous carcinoma and the large adenocarcinoma which in some instances may have invaded the greater part of the gastric wall and still not have extended grossly beyond the stomach except for involvement of the regional lymph nodes along the two curvatures. b) Small lesions situated high on either curvature or on the anterior or posterior wall in such a manner as to make adequate resection impossible except by removal of the lower end of the esophagus. c) Sessile or polypoid lesions occurring in the lower or middle portion of the stomach but with indefinite intramural extension cephalad as evidenced by thickening and friability of the gastric wall proximal to the lesion.

Neither the size of the lesion, nor age of the patient should be considered a contraindication to the study and surgical treatment of these patients. Post mortem examination of subjects dying of untreated gastric cancer in reported series from the time of William Welch to the monographic report of Livingston and Pack<sup>11</sup> shows a constant figure of 20 to 25 per cent of these patients with the cancer confined to the stomach without demonstrable microscopic evidence of metastases.

#### SUMMARY AND CONCLUSIONS

In a study of fifty-seven patients with gastric cancer, 40.2 per cent showed either primary or secondary involvement of the cardia with the neoplastic process. Neither symptoms nor laboratory studies were of value in recognizing these lesions except roentgen-ray and gastroscopy.

In ten patients, or 17.5 per cent of the entire group, malignant involvement of the cardia was recognized by gastroscopy alone. Of the six cases with a primary lesion, five were diagnosed by gastroscopy alone. In five additional cases with involvement of the cardia not recognized on roentgen study, obstruction was encountered when gastroscopy was attempted.

These figures emphasize the clinical frequency with which the cardia of the stomach is involved by neoplasm and the means of diagnosing it.

An accurate preoperative recognition of the location and extent of gastric cancer is essential to proper treatment, particularly if total gastrectomy is to be performed effectively.

#### ADDENDUM

Since submitting this paper for publication an additional 125 patients were examined gastroscopically. Of this group twenty-four had neoplasm of the

stomach; in thirteen there was primary and in five secondary involvement of the pars cardiaca, while in six only the body and antrum were involved. Of those patients with involvement of the pars cardiaca the nature of the lesion was questionable on roentgen study in three and in three others obstruction at the cardia prevented the lesion being seen gastroscopically.

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## GASTRIC DIAGNOSIS IN RETROSPECT\*

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"History is the witness of the times, the torch of truth, the life of memory, the teacher of life, and the messenger of antiquity."—Cicero

I imagine that many of you who, like the writer, have wrestled with the problems of gastric diagnosis, so these many years, have had the desire to record, weigh and appraise the lessons of the past in the light of present progress. Suffice to say that the invitation to address you has provided me with the necessary stimulus to undertake such a modest, perhaps worth-while task. Obviously, a comparison of the experiences of the period antedating roentgenology and endoscopy, the former in particular, with those of the following period, is the logical approach to our thesis. While such consideration might appear academic to some of my listeners, it has proved fascinating and instructive to me personally.

It was my good fortune to be closely associated for years with those American pioneers of gastric surgery and diagnosis, the Drs. Mayo and Dr. Christopher Graham. The contributions of W. J. Mayo, dating back to 1894, dealt with advanced gastric carcinoma and obstructing juxtapyloric benign lesions which permitted of easy diagnosis. Dr. Graham's first paper on gastric ulcer appeared in 1903, and another on duodenal ulcer appeared the following year. The primitive state of diagnosis by means of laboratory methods at that time was characterized in a statement by my late chief, Dr. W. J. Mayo in 1903: "I do wish to call the attention of the general practitioner to the fact that the refinements of technical diagnosis are often useless and occasionally harmful in causing delay, and that the sensible practitioner, with the few simple means at his command, is perfectly capable of arriving at a reasonable diagnosis, and will at least be able to direct the majority of his patients needing surgical treatment to the surgeon in time to be benefited."

In the interval between this early period and 1913, when the late Dr. Carman became a member of the staff and embarked on a distinguished roentgenologic career, hundreds of patients with gastric and duodenal ulcer underwent operation. During that period diagnostic procedure was largely that of careful and thorough anamnesis in the majority of cases, physical examination and gastric analysis playing a secondary role. Among the fruits of that era were the contributions by Moynihan and by my senior medical and surgical colleagues to our present knowledge of the symptomatology, incidence and pathology of chronic peptic ulcer, the importance of which is undimmed by the passing years.

\* Read before the American Gastroscopic Society, Atlantic City, New Jersey, May 2, 1948.

Even during the developmental period of roentgenology we had to rely continuously on time-honored methods of diagnosis in doubtful cases. Some of you will recall that this period was marked by a difference of opinion among leading roentgenologists regarding the respective virtues of roentgenoscopic examination and indirect signs and serial roentgenology, especially with reference to the roentgenologic diagnosis of ulcer. Eventually, the opposing views of both camps were reconciled and thereafter progress in roentgenologic diagnosis of diseases of the alimentary canal was rapid.

In the period before roentgenologic examination was available, the only preoperative positive evidence of the presence of gastric carcinoma was the occasional finding of malignant tissue removed during aspiration of the gastric contents. This was a relatively infrequent occurrence, and rare in the early stages of the disease. On occasion the growth was visible through the esophagoscope or the nonflexible gastroscope of an earlier vintage. Advanced disease, with tumefaction and variable degrees of pyloric obstruction or gastric retention, taken in conjunction with the often telltale findings on gastric analysis, gave rise to few preoperative diagnostic errors. But it was that group of cancer-bearing patients who were of good flesh and color, without palpable mass or gastric motor dysfunction and with no suggestive findings on gastric analysis, that frequently gave rise to great concern on our part. On one such occasion, Dr. Plummer and I filled the patient's stomach with a bismuth mixture and thereafter, even with our unpracticed eyes, were able to detect a distinct filling defect on the roentgenograms. The presence of carcinoma of the pars media and lesser curvature was confirmed by operation a few days later. This episode impressed my senior colleagues with the reliability and dispatch afforded by roentgenologic examination and steps were immediately taken to fill this vacuum in our diagnostic procedure.

It is not necessary to tell this audience that gastritis in the late eighties of the last century and early part of the present century, apart from that in association with pernicious anemia, was a rather nebulous entity. However, there were some who were not lacking in courage, if not in discretion, in venturing such diagnosis. Franklin White, in his recent admirable address commemorating the fiftieth anniversary of the American Gastroenterological Association, made the following observation: "We can afford to smile at some of the early papers, of thirty or forty years ago. For example, we find forty-five years ago 'Study of 600 cases of Gastritis and Treatment with Sprays and Powders.' " While the diagnosis "chronic gastritis" was often made, up to recent years actual proof of its existence was usually lacking. Such a diagnosis was too frequently used as a diagnostic catchall or a face-saving gesture. Actually, bona fide cases of the acute variety of the disease, including phlegmonous gastritis, were almost exclusively restricted to the fatal form, and confirmed only at necropsy, or

occasionally in the surgical amphitheater. This was also true of the chronic forms which were invariably a complication of, or in association with, some more serious pathologic process. Up to recently, interest in and study of gastritis, in association with the familiar gross lesions of the stomach and duodenum, were treated in rather a stepfatherly fashion by the rank and file of American surgical pathologists. But a growing appreciation of, and increasing resort to, gastroscopy in this country has changed all this. Even the present-day roentgenoscopic examination presupposes a routine preliminary study of the mucosal relief, as a result of which the wise roentgenologist often requests a gastroscopic examination because of the presence of some actual or apparent mucosal abnormality.

In this welcome era of visualization methods of diagnosis, what are the changes that have been wrought? Perhaps, first of all, should be mentioned the value of the "negative stomach," roentgenoscopically speaking. Such a finding is of great advantage in the saving of time and money by the avoidance of misdirected medical or surgical treatment, in view of the fact that the symptoms of organic gastroduodenal lesions, peptic ulcer in particular, may be mimicked by a large variety of conditions, as you well know. Of course it must be remembered that a small percentage of lesions can never be visualized and that the presence of a lesion in the early stages may escape detection on the initial examination. The same may be said of a normal cholecystographic response. Prior to the advent of cholecystography we all knew how many normal gallbladders were removed by the best of surgeons on the basis of an erroneous diagnosis. While a normal-appearing cholecystogram does not exclude actual cholelithic disease, a cholecystectomy nowadays is certainly not indicated unless the clinical evidence is overwhelming and unless the exclusion of a variety of other conditions which could simulate cholelithic disease in whole or large part has been made. Among such conditions I should like to mention briefly hiatal hernia. Imagine the difficulty of diagnosing that by no means infrequent entity without roentgenologic aid! By the same token, unwarranted operations upon the stomach also have been greatly reduced and discouraged. Some of my listeners can recall Von Eiselsberg's indictment of "concession gastroenterostomy" of an earlier period. The significance and frequency of a "negative stomach" in spite of a history of gastroenteric hemorrhage, and the restraint such finding imposes upon the surgeon, is now a matter of general knowledge.

Secondly, equal in importance to such negative roentgenologic findings, and in a sense more dramatic and significant, if by no means as frequent, is the visualization of a lesion in the stomach or its continuations. The former ever recurring problem of location, extent, depth and such complicating factors as hourglass deformity, accessory pocket, impaired or accelerated motor

function, associated spastic phenomena and dilatation or contraction of the organ, was resolved in one fell swoop. On the heels of this salutary development followed other diagnostic achievements, such as the demonstration of multiple gastric lesions and their possible nature, coexisting gastric and duodenal lesions, the meniscus sign complex, which is so important in the recognition of ulcerating carcinomata of whatever size, and the fruits of studies of mucosal relief.

In the third place, the disclosures in the roentgenologic examining room revealed our former unfamiliarity with the not infrequent atypical forms of gastroduodenal ulcer from the standpoint of symptomatology, to say nothing of the benign masquerades of gastric carcinoma, the asymptomatic nature of benign tumors of the stomach, duodenum and small bowel, apart from anemia, and gross or occult bleeding. Time does not permit me to go into a detailed consideration of this intriguing phase of the subject.

While much continues to be written about the problems of gastric diagnosis in patients who have never undergone operation on the organs of the digestive system, the general clinician or gastroenterologist of wide experience realizes only too well that our most difficult field, frequently taxing all our diagnostic and therapeutic resources to the utmost, is the one concerned with late sequelae of gastric surgical treatment. Here the possibility of recurrent ulceration, disturbances of motility through mechanical derangements for one reason or another, significant morbid physiologic and nutritional changes, psychoneurotic state, singly or in variable combinations, may be present. In the absence of concrete knowledge concerning the nature of the original lesion, if any, the type of operation carried out, the skill and experience of the surgeon or the nature of any possible early postoperative complication, the internist must depend much upon what roentgenoscopic and gastroscopic examinations reveal. Even then careful observation in the hospital may be necessary. Without such modern technics how else could the medical consultant detect with certainty, short of exploratory incision, the normal luminal outline of the stomach and duodenal bulb, which is strongly suggestive that the operation was unnecessary, dysfunction of the gastroenteric stoma or jejunal loop, defect in the gastroenteric stoma, a grave technical error such as a gastro-ileostomy, or the presence of a diffuse or the more circumscribed perianastomotic form of gastritis? Revealing as such diagnostic aids usually are, one must be cognizant of certain inherent difficulties following operation which I shall point out shortly.

In my opinion a gastroscopic examination is indispensable in the detection of gastritis in all its forms, whether primary or secondary. The frequent association of gastritis with gross benign and malignant lesions of the upper part of the digestive tract and the important role such lesions may play in

late postoperative sequelae are now a matter of record. Gastroscopic examination also is singularly effective in the visualization of acute and chronic shallow gastric lesions which may give rise to pain or hemorrhage, in most reliably assessing the effects of treatment and frequently in determining the malignant nature of a circumscribed ulcerative or small tumefactive lesion; and while on the subject I am reminded of the value of esophagoscopic examination in confirming the roentgenologic diagnosis of a hiatal hernia and the presence or absence of inflammation (esophagitis), ulceration or cicatrization.

From the foregoing observations one might wonder how we carried on as well as we did in the period antedating these modern technics. However, I feel confident that those of you whose clinical training was contemporaneous with my own are better clinicians on that account, so that you are not slavishly dependent on laboratory methods, which often may fail. Through sheer necessity you have developed the art of thorough and concise history taking and meticulous physical examination. In other words, you have made, and continue to make, proper use of brain, eyes and hands, which are just as essential to successful diagnosis today as in the past. I fear that recent generations may not be sufficiently mindful of this fact.

Some one has well said that there is no royal road to diagnosis. There will always be errors of omission and commission, even on the part of the most expert roentgenologist or endoscopist, which errors are increased when he is working under pressure or is unduly fatigued. As previously stated, a small percentage of lesions are not possible of visualization. When laboratory findings are not consistent with the clinical evidence the circumspect clinician takes nothing for granted. Just as the "negative stomach" may not exclude the presence of an active ulcer, a bulbar deformity, for example, does not necessarily imply the presence of an active ulcer. A juxtapyloric lesion in association with a significant barium residue, but without associated visible filling defect, would make consistent a roentgenologic diagnosis of obstructing duodenal ulcer even though the clinical evidence may point overwhelmingly to an obstructing carcinoma. And there may be frank clinical evidence of gastric retention when the roentgenologic examination and barium motor meal fail to confirm it. Clinicians have also pointed out that the complete disappearance of an ulcerous lesion after treatment does not necessarily imply its benignancy. The possibility of misinterpretation of roentgenologic findings after operation on the stomach is even greater because of defects produced by the operation itself which may be indistinguishable from actual lesions. Stomal ulcers frequently fail of detection; however, the frequent demonstration of a malfunctioning gastroenteric stoma, coupled with the clinical evidence, usually makes a positive diagnosis of such a lesion logical.

As regards gastric carcinoma, a gastric defect due to persistent spasm oc-

casionally is the cause of erroneous diagnosis. A lesion on the posterior wall and pars cardiaca, so-called high-lying cancer, can easily be overlooked, although the anamnesis and results of gastric analysis strongly point to its presence. In carcinomas thus located, with the exception of the scirrhouous type, Miss Sawyer has repeatedly called our attention to the momentary obstruction at or below the level of the cardia on passage of a 14 F. Sawyer tube. The stomach is quite empty although there are remnants of the test meal admixed with mucus and small amounts of blood due to oozing from the ulcerated surface. Often there is an associated fetid, foul, rather fleshlike odor to the small volume of contents aspirated. Such findings are highly suggestive of the presence of a high-lying lesion, occasionally overlooked on the initial roentgenoscopic survey, the presence of which, however, is almost invariably corroborated on repeated roentgenologic or gastroscopic examination.

With considerable gratification I have already pointed to the diagnostic advantages peculiar to gastroscopy, but such procedure, like roentgenoscopy, may fail us at times, for reasons best known to this audience. From my own observation the difficulties encountered are those abnormalities, congenital and acquired, which preclude passage of the tube, the presence of so-called blind areas which makes visualization of the involved area difficult or impossible, the presence of mucus, food or fluid, which interfere with proper examination, and so forth. Even if the lesion is visualized, the interpretation of its exact nature may be equivocal or impossible in the absence of biopsy. And last but not least, it must always be remembered that the most significant and frequently occurring gross lesion, namely duodenal ulcer, is beyond the reach of the instrument, to say nothing about the difficulties of visualization of a juxtapyloric lesion, especially a benign one.

Regardless of the achievements of reoentgenoscopic and endoscopic methods of diagnosis, for which we internists are duly grateful, and regardless of the few shortcomings which I have pointed out and of which we are more or less cognizant, both procedures should be regarded by their proponents as complementary and not competitive, as one of your members so wisely stated recently. Unwarranted claims and undue enthusiasm for the endoscopic method will do much to discredit a deserving technic which has so much promise for the future. The restraint manifested in more recent contributions and texts on gastroscopy is commendable. It is also gratifying to realize that the great majority of the members of your organization are first of all internists or surgeons, which makes for progress, proper perspective and "thought processes not limited to the internal boundaries of the peritoneal cavity."

## FLEXIBLE TUBE ESOPHAGOSCOPY

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The value of esophagoscopy as a diagnostic procedure has long been established. Its importance in the recognition of esophageal disease or neoplasm, as well as local manifestations of general disease, removal of foreign bodies, biopsy, application of local treatment, surgical removal of tissue and the dilatation of stricture is universally accepted.

Unfortunately, the passage of an esophagoscope in the past has been limited to those, who by virtue of special training and skill were able to carry out this difficult procedure, and not without oft felt fear and trepidation have patients been subjected to such an examination. For the ordeal of instrumentation echoed its dangers in a not so infrequent calamity—which left memories to both family and physician alike.

Dangers inherent in anatomy and function underlie the problems of technique. Broyles said "No attempt should be made to pass a rigid esophagoscope in a patient until the operator has familiarized himself with the normal anatomy of the region and has become accustomed to the use of the instrument by passing it on dogs and cadavers". Clerf underscored the importance of direct vision in carrying out the procedure, which represents the general view of endoscopists employing rigid tubes to-day. That the esophagus is surgically one of the most intolerant viscera in the body has been justly recorded by Jackson. He stated further, "Passing the cricopharyngeus muscle is the most difficult and dangerous part of esophagoscopy—anaesthesia helps little if at all". With a stiff instrument, were pressure to be exerted blindly against the pharynx rather than along the natural passageway through the pyriform fossa, the esophagoscope will go into the mediastinal tissues with probably fatal consequences. A mere microscopic tear may be the starting point for the invasion of microorganisms with resultant mediastinitis.

How can the difficulties and dangers of esophagoscopy so universally recognized be overcome? Can the technique of instrumentation be so simplified as to encourage its more widespread use by insuring greater comfort and safety to the patient as well as facility to the examiner?

The answer is in the affirmative and is the result of efforts extended along the line of overcoming the main hazard to instrumentation of the gullet, the cricopharyngeus muscle. This is the bulwark that has to be traversed and if accomplished with simplicity and without trauma, the avenue of approach beckons to the effortless completion of the attempted diagnostic or therapeutic endeavor.

The feature of the new instrument is embodied in the softness and extreme morsability of its spiral tip. It must be stated in all frankness, that material shortages and manufacturing difficulties have left much to be wanted in the attainment of the goal envisaged, a strong durable tip. It is hoped, very shortly, to be able to announce its completion and presentation in conformity with proper specifications. In no small measure have these production difficulties stood in the way of further research and progress. And yet in the face of these obstacles, even at times working with imperfect units, it has been possible to effect *safe, easy, successful* esophagoscopies in over 350 patients. This work has been carried out at the New York City Cancer Hospital, Bronx Hospital and Bellevue Hospital.

Patients were chosen at random, only those with hazardous contraindications being excluded as prospects. In this way a truer assessment of the technical advantages and limitations were hoped to be achieved. Age was no drawback although extreme debility was regarded as such. Subjects with lung tumor, tracheal distortion, pleuritic effusion, high or low lying esophageal lesions, mediastinal tumor, etc. were listed as subjects of intubation. Indeed, some with old electrocardiographic changes were included. And this went on, not without that uneasy feeling, which only the joy of accomplishment could satisfy. Emphatically, this citation is by no means recommended as a guide to indications for the procedure.

In only six instances out of this number was it not possible to effect a satisfactory technique. Two of these could neither understand nor speak English and in consequence could not be prevailed upon to keep their mouths open nor their tongues out. One patient refused to swallow, and the remaining three presented high lying lesions which interfered with the insertion of the instrumental tip. As for the rest, no difficulties whatsoever were encountered in passing through the pharyngeal pinchcock, each case—adding to the delight of the previous one.

#### TECHNIQUE

A word or two of warning first: The choice of patients should exclude those with fever, bad hearts, dyspnea, aneurysm and extreme debility. A high lying lesion is a contraindication to the introduction of the flexible esophagoscope. Visual guidance at the outset is indispensable in such patients. These are however in the minority.

The patient receives neither food nor drink on the morning of the examination. Two successive doses of one and a half grains of luminal are administered hypodermically at one hour intervals to be followed in a half hour by one fourth grain of morphine sulphate and one hundredth grain of atropine sulphate. One-half hour later the throat is sprayed with 10% cocaine without

adrenalin, which is repeated again after five minutes. The patient is then subjected to a lecture consisting of a few honeyed words of relaxation; the sweeter the better. This is *important*. So much so that if it is unimpressive or omitted, it will invariably guarantee a rough session.

With the patient lying on his left side (the Schindler position) and his head resting on a pillow as first suggested by Benedict, the flexible tip is guided into the mouth towards the pharyngeal wall. The patient is told to swallow and simultaneously pressure of the instrument is effected as the head is extended by the assistant. No forcing is attempted or required. Should there be some pharyngeal resistance, a few words of appeasement will be followed by relaxation and easy penetration of the pinchcock. The patient is either left in this left sided position or rolled over on his back. In the latter case, the edge of the table should lie astride the middle of his scapula, permitting free movement of the head by the assistant as directed by the operator. The straightening combination, consisting of an open cannula and olive tipped trocar is inserted into the lumen as a to and fro movement of the outer tube favors installation of the latter. The obturator is finally withdrawn leaving the outer tube and rigid cannula *in situ* through which visualization and instrumentation may be accomplished. Deeper insertion into the gullet takes place under direct visual guidance. As the lower esophagus is reached, especial care is exercised, for the organ veers anteriorly and to the left. A partial withdrawal of the straightening cannula reestablishes a pliable tip which can readily be insinuated into the gastric cavity. Angulation of the plane of the stomach with that of the esophagus imposes at times a formidable obstacle to the introduction of the rigid cannula into the lumen of the scope in this region. Under no circumstances is force to be used. At the completion of the examination the instrument is withdrawn, during which continued inspection of the interior of the swallowing tube is carried out.

It is not to be assumed that employment of the flexible esophagoscope implies blind introduction. Visual aid is relied upon at the earliest possible moment. One cannot see around curves unless a lens system is used. Such is not resorted to in this instrument. At the earliest opportunity the instrument is brought into a straight line as described. This is accomplished just as soon as the cricopharyngeus is penetrated. Let us contrast this procedure with a description of instrumentation with the rigid tubes as described by Jackson. "The instrument is guided into the right pyriform sinus for 2-3 cm. (under guidance of the eye) when it comes to a full stop *and the lumen disappears*. This is the tonically closed crico-pharyngeus. Moderate pressure is now made against the (closed) muscle and after a few seconds or a minute or two of waiting a lumen (*usually*) appears. *A filiform bougie may have to be inserted to make sure of a lumen ahead*". As can readily be seen,

the rigid tube protagonists do confront situations where vision alone does not suffice. Points of anatomic arrest present themselves from time to time, when probing for direction is essential, and not too rarely has a general anaesthetic to be resorted to for the fulfillment of a successful procedure.

At no time, in over 350 esophagoscopies has there been any need for the use of filiform bougies or general anaesthetics while using the flexible tube. Up to the time of the development of the flexible esophagoscope, instrumental exploration of the gullet could only be accomplished by the expert. Many an aspirant in this field of endeavor was constrained to forego his ambition in this line because of failure and misfortune. As a result, the limited few, in whose hands this important method reposed were soon found outside the pale of the gastroenterologist, and esophagoscopy assumed the aspect of a superior surgical approach. The intimate position of this type of manipulation in the field of gastroenterology was kept alive by a few skilled and adventurous workers—namely Schindler, Paulson, Benedict amongst others. They were able to master the imposing technical difficulties, combining their skill on the one hand with their knowledge of gastroenterology on the other. It is palpably apparent, that no attempt is made to revolutionize or disrupt so called spheres of influence or activity or in any way harness methods outside of the realm of the gastroenterologist. It is intended however, to simplify the activities of the latter as well as that of the endoscopist and most important of all to insure comfort and safety to the patient.

Anyone who has passed a flexible gastroscope will find it just as easy to insert a flexible esophagoscope and with equal safety. Internes, after a single demonstration have succeeded in doing so. This does not mean that rough handling or reckless abandon would not invite calamity. Any obstacle to the free and easy passage of the instrument calls for an interruption of the process. At no time is forcing to be countenanced. Sterility of instruments must be maintained.

Today we stand on the threshold of a new dawn in the exploration and treatment of diseases of the esophagus. This is my earnest and considered opinion. The practicability, safety and ease of esophagoscopy by means of this new flexible esophagoscope has been amply demonstrated. At the present time, there remains a mere question of minor manufacturing details of a mechanical nature. A much more durable instrument than the ones originally experimented with have been promised by the manufacturer and will be available shortly. With its use, there unfolds before us a wide expanse, a fertile field, no longer to be feared and avoided, but one urging more and more endeavor.

## THE COMPARATIVE BUFFERING CAPACITY OF INTACT AND PRE-DIGESTED PROTEIN\*

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### INTRODUCTION

In a previous study, Siler and I<sup>1</sup> demonstrated the intragastric buffering of gastric acid by a solution of a protein hydrolysate.<sup>†</sup> Later, I<sup>2</sup> reported the excellent results obtained with its use in the treatment of bleeding peptic ulcers. Shortly afterwards, Co Tui and his associates<sup>3</sup> stated that the pH and acid values in their cases "were in good agreement with Siler and Levy" and demonstrated the beneficial effects of protein hydrolysates when used in the treatment of intractable peptic ulcers. More recently, Hodges<sup>4</sup> reported that the use of a hydrolysate "appeared more efficacious than a conventional dietary program in producing a remission." He further stated that "in every instance, the gastric content was rendered free of ionizable hydrochloric acid as determined by Toepfer's reagent.

Free hydrochloric acid remained absent for an average of 70 minutes, the range being from 30-120 minutes." Kenamore and his co-workers<sup>5</sup> concluded that increasing the protein content of the diet produced more rapid improvement in peptic ulcers and that the protein hydrolysate used was effective in maintaining nitrogen balance and producing relief of pain. On the other hand, Rossein<sup>6</sup> found that, "while the hydrolysate rendered the gastric contents free of hydrochloric acid, there was a later rise above the fasting levels."

Bockus<sup>7</sup> stated that "the buffering action of the amino acid mixture under discussion is not uniform in all patients and the antacid value of the newer hydrolysates remains to be tested. There is no proof at hand to indicate that the buffering action of the protein hydrolysate administered every two hours as originally advocated by Co Tui is superior to or even as efficient as the neutralization of gastric acidity which is accomplished by the orthodox ulcer management. Little is known of the secondary gastric secretagogue effect of various amino acids mixtures now commercially available."

### METHODS

In order to clarify the value and limitations of a protein hydrolysate in the treatment of peptic ulcer, several studies have been instituted at the University

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† Amigen, Mead Johnson Company.

of Arkansas School of Medicine. The first of these is being presented today. It was decided to re-investigate the buffering capacity of a hydrolysate; namely, "protolysate." Twenty patients who had a good response to the secretory stimulus of histamine were selected for the study. The diagnoses in the twenty cases were; eight had no disease, duodenal ulcer two, pyloric ulcer one, diverticula of the duodenum two, schizophrenia in remission two, hypertension one, recovery after pneumonia one, rheumatoid arthritis one, latent syphilis one, and chronic alcoholism one. The histamine was injected subcutaneously in a dose of 0.1 mg per 10 kilo of body weight. A Levin or Rehfuss tube was passed in the morning after a 12 hour fast and fasting contents emptied. The position of the tube was checked by fluoroscopy. The histamine was injected and aspirations made every ten minutes for ninety minutes. Then the stomach was emptied, lavaged with normal saline, again emptied in 15 minutes and a second injection of histamine given. The same number of aspirations was made again. The gastric contents were tested for free acid by titrations with N/10 NaOH, using Toepfer's reagent for the indicator; for total acidity using phenolphthalein for indicator; for pH using a quinhydrone potentiometer for the determinations. On the second morning, the patient was given 300 cc of a 10% solution of protolysate to drink at the same time the histamine was injected. After the ninety minutes aspiration, the stomach was emptied and washed out with saline. Fifteen minutes later the stomach was aspirated again and the test was repeated using 300 cc of milk. On the third morning the patient was given 300 cc of a 10% mixture of pure casein in water at the time of the histamine injection. The different solutions were drunk by the patient to avoid any remaining in the tube and thus possibly affect the findings. Rivers, Osterberg, and Vanzant<sup>8</sup> have shown that a second injection of histamine will be followed by secretory response similar to the first. In this series, a second injection produced a secretory response which compares very closely with the first one (Fig. 1).

#### RESULTS

Protolysate completely buffered free acid for 30 minutes in all instances; milk only for 10 minutes. Casein failed to buffer two of the twenty cases in the ten minutes period and the number of instances without free acid fell rapidly thereafter. All of the protolysate group showed an absence of free acid at 30 minutes, as compared to 12 of the milk group and 9 of the casein group. At 40 minutes, 16 of the protolysate group as compared to 5 of the milk and 6 of the casein groups showed an acidity. At 50 minutes, the comparison continues to demonstrate better buffering by pre-digested protein. After this time period there is not any significant difference. Comparison of the pH values reveals a similar picture (Fig. 2). In this study, free acid was

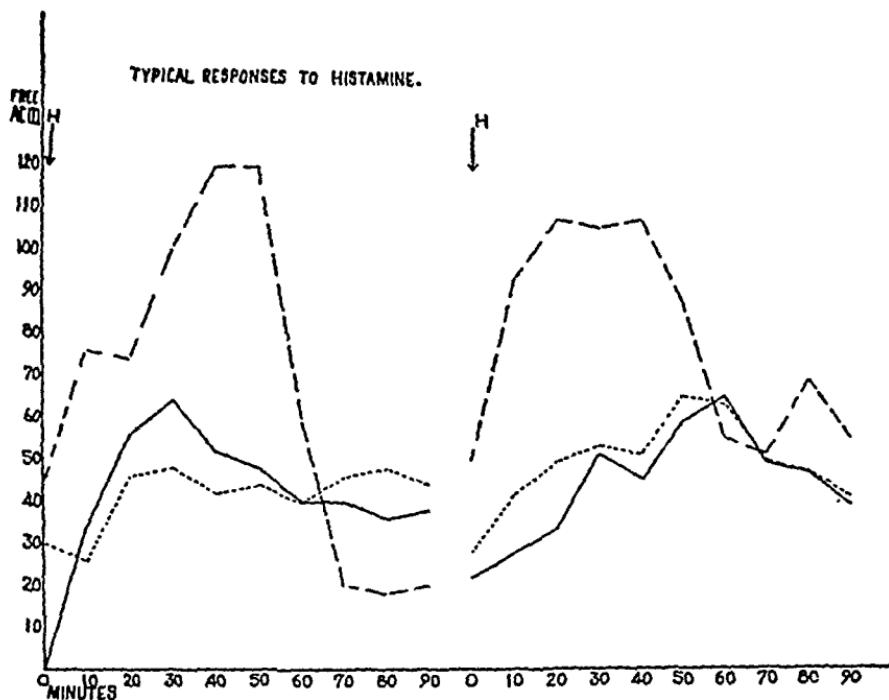


FIG. 1. TYPICAL RESPONSES TO HISTAMINE

H indicates injection of histamine. The secretory effect of the second injection closely follows the first.

CHART 1  
*Cases without free acid at each aspiration (20 subjects)*

	10	20	30	40	50	60	70	80	90
H	1	0	0	0	0	0	0	0	0
P	20	20	20	16	11	7	5	4	4
M	20	19	12	5	3	3	3	3	2
C	18	14	9	6	5	3	4	3	3

## Note:

H = Group receiving histamine only.

P = Group receiving histamine and protolysate;

M = histamine and milk;

C = casein and histamine.

absent in all instance when the pH was 3.0 or above except in four aspirations, all in case 2. The protolysate group maintained a higher pH longer than either of the intact proteins.

Hollander<sup>9</sup> proposed the term "proteolytic neutralization point" for that pH at which pepsin activity is lost. This is a pH of 5.0. However, he states

that at pH of 4.0 there is but 10% of peptic activity remaining. It is to be noted that protolysate maintains the pH at the higher values closer to this proteolytic end point for longer periods of time than either milk or casein, even though the latter may also show an absence of free acid. It is of interest to note that the average pH value at 90 minutes was practically the same with both the protolysate and the milk groups indicating that they have equivalent secretagogue effect.

A statistical study of the data further establishes the significance of these observations. Comparison of the standard deviation (Chart 2) at each time

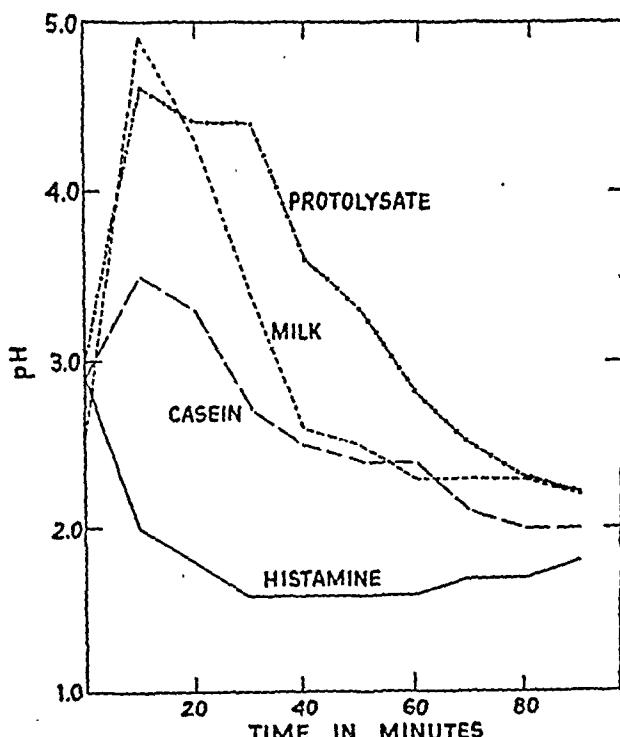


FIG. 2. THE ABOVE CURVES REPRESENT THE AVERAGE pH AT EACH ASPIRATION PERIOD IN EACH GROUP

It is to be noted that the pH at 90 minutes is the same in the protolysate and the milk groups. interval for each of the substances used reveals that this deviation is about equal, indicating an equal variability of the data. Chart 3 is a summation of the statistical data designed to show whether or not the differences are significant. Any value of 3.0 or greater indicates a statistical significance; or as expressed in terms of chance, if the value is 3.0, the chance of there being no difference between the two compared averages is only one in one thousand. In this chart we have compared the differences in the average free acid and pH values for protolysate, milk and casein. At the 30 minutes period, therefore, there is a value of 3.0 or greater indicating a statistical difference between

## CHART 2

*Average values and standard deviation of free acidity and pH at each aspiration period*

The similarity of the standard deviation of each group indicates the variability in the data is comparable.

	PROTOLYSATE		MILK		CASEIN	
	Avg.	S. D.	Avg.	S. D.	Avg.	S. D.
Free Acidity						
F	20.6	22.1	22.6	18.5	18.5	18.2
10	0	0	0		1.9	6.4
20	0	0	1.8	7.8	3.1	5.0
30	0	0	7.0	9.1	17.0	18.6
40	8.6	19.5	23.5	21.7	27.2	21.5
50	21.9	27.7	22.5	22.5	35.3	26.6
60	38.6	31.1	38.8	25.9	41.1	30.3
70	20.5	33.6	31.9	21.3	43.8	30.8
80	56.8	33.8	31.6	20.5	43.1	28.0
90	52.8	31.7	34.4	20.7	47.4	30.6
pH						
F	3.0	1.58	2.5	.95	2.9	1.13
10	4.6	.65	4.9	.99	3.5	.57
20	4.4	.70	4.3	.97	3.3	.76
30	4.4	.64	3.4	1.35	2.7	.98
40	3.6	.78	2.6	1.12	2.5	.89
50	3.3	.90	2.5	1.18	2.4	1.11
60	2.8	.87	2.3	1.04	2.4	1.27
70	2.5	.82	2.3	.96	2.1	.84
80	2.3	.83	2.3	.90	2.0	.75
90	2.2	.79	2.2	.78	2.0	.84

## CHART 3

*Significance Ratio: A statistical analysis of the comparison of the differences in the free acid and pH values for Protolysate, Milk and Casein*

TIME	FREE ACID		pH	
	Milk	Casein	Milk	Casein
Fasting	.3	.3	1.2	.2
10	.0	1.4	1.1	5.5
20	1.0	2.8	.4	4.8
30	3.5	4.0	3.0	6.5
40	2.3	2.9	3.3	4.2
50	0.1	1.6	2.4	2.8
60	.0	.2	1.6	1.2
70	2.1	.6	.7	1.5
80	2.8	1.4	.0	1.2
90	2.2	.5	.0	.8

Protolysate and milk, either when measured by the free acid or by pH. There is an even more significant difference between Protolysate and casein and thus between predigested and intact protein.

The fasting free acidity in all cases ranged from 0° to 86° with an average of 20°. The free acidity was higher than the fasting after 50 minutes in each group. At 90 minutes, the free acid of those receiving histamine alone ranged from 10-96 with an average of 45 degrees; in the protolysate group the range was from 0-110 with an average of 52 degrees; in the milk group, the range was from 0-84 with an average of 36 degrees; in the casein group, from 0-94 with an average of 48 degrees.

It is to be noted that there is a higher free acid value at 90 minutes with Protolysate than with the other two materials, but that the pH values were identical. There is no significant difference, statistically speaking, between any of the values since our significance ratio is consistently less than 3.0.

CHART 4

*Number of cases whose free acid at 90 minutes was higher than the fasting free acid (20 subjects)*

H	P	M	C
18	13	13	15

H = Histamine alone.

P = Histamine and protolysate.

M = Histamine and milk.

C = Histamine and casein.

Thus, there is no basis for concluding that at 90 minutes at least, predigested protein has a greater gastric secretagogue effect.

#### COMMENT

In our first report, Siler and I stated that Amigen, which was the hydrolysate used, buffered free acidity for a significant period of time. The observations (Fig. 2) reported here confirm this statement even in the presence of the strong and uniform stimulus to gastric secretion afforded by the injection of histamine. The present findings indicate that at least one of the protein hydrolysates, namely protolysate, is a satisfactory antacid.

Kirsner and Palmer<sup>10</sup> reported a pH range of 1.51 to 1.48 following hourly feedings of milk and cream. They increased the protein content with casein but altered the pH values but slightly. They stated that increasing the protein content of the feeding did not elevate the gastric pH. The present observations, also, indicate that fortifying the milk with casein would not be an effective method of raising the pH of the gastric contents. On the other hand, it is indicated that a pre-digested protein would be more effective. A

study of the gastric pH throughout the day following the ingestion of milk and cream and protolysate is now in progress.

The orthodox plans of ulcer management mentioned by Bockus call for hourly feedings with, in most instances, antacids given between these hourly feedings. On the basis of our first findings<sup>1</sup>, I used the hydrolysate as an antacid as well as a protein on an hourly feeding schedule in the usual "orthodox" manner. The results in treating bleeding peptic ulcers were very satisfactory as I reported.<sup>2</sup> The present observations also suggest that the hydrolysate be given on a hourly schedule and not on the two hourly schedule as used by Co Tui and his group. In this way the maximum buffering effect of the hydrolysate is better utilized.

The main advantage of a nitrogenous preparation over the chemical antacids is the increased protein intake made possible by such substances. My own observations (to be reported) are in full accord with those of Kenamore, Hodges, Co Tui and others of the value of an increased protein intake, even though the ulcer patient may not show a definite clinical protein deficiency. Such deficiencies are difficult to define. One of the striking effects I have noted is the *increased sense of well being and an ability to do a full day's work* which the patient taking the hydrolysate reports. A positive nitrogen balance is necessary for protein regeneration. We must supply the building stones necessary to form new protein tissue and to heal the ulcer. By using a pre-digested protein, such as Protolysate, we supply an effective antacid and, also, a material necessary to cure the lesion.

#### CONCLUSION

1. The observations reported here confirm the previous reports of the efficiency of the buffering capacity of an enzymatic hydrolysate of protein.
2. The protein hydrolysate employed was more effective under the conditions of this experiment than either milk or casein in producing high pH values of the gastric contents.
3. Gastric acidity was uniformly higher at 90 minutes than in the fasting contents after the ingestion of either milk, casein, or the hydrolysate. This suggests that these three substances have equivalent secondary gastric secretagogue effects. In other words, the pre-digested protein (Protolysate) did not exhibit any greater secondary secretagogue effect on gastric secretion than the intact proteins (milk and casein).
4. Observations on gastric chemistry after hourly feedings during the day are now in progress.

The author wishes to express his thanks and appreciation to Mrs. Jean Meisenbacker for her technical assistance and to Dr. Warren M. Cox, Jr., for his statistical analysis of the data.

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# THE COMPARATIVE EFFECTS OF CASEIN HYDROLYSATE, MILK AND MILK-CREAM ON GASTRIC AND DUODENAL BULB ACIDITY IN DUODENAL ULCER PATIENTS\*

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## INTRODUCTION

Hydrolyzed protein has been advocated as a valuable adjunct in the treatment of both simple and complicated gastroduodenal ulcer.<sup>1-10</sup> Among the advantages claimed is an excellent buffering action.<sup>9, 11-14</sup> The observations thus far reported, however, have been confined to the stomach. The methods of study have varied and the conclusions drawn have not been in entire agreement. Moreover, not all of the subjects have had a chronic gastric or duodenal ulcer. Much information is still needed, therefore, before the buffering capacity of hydrolyzed protein can be properly evaluated as a factor in ulcer management.

The studies reported herein were undertaken: (1) to observe the effects of an aqueous mixture of casein hydrolysate, dextrins and maltose on the acidity of the contents of both the duodenal bulb and pars pylorica in patients with active duodenal ulcer; and (2) to compare these effects with those of milk and a mixture of milk and cream.

## MATERIAL

Eleven patients with clinical and roentgenologic evidence of duodenal ulcer were selected from the wards and Gastro-Intestinal Clinic of the Graduate Hospital of the University of Pennsylvania. Symptoms had been present for from slightly more than 1 year to approximately 20 years. All had symptoms indicative of active recurrent ulcer at the time, or up until a few days before, studies were performed. Seven showed roentgenologic evidence of an ulcer fleck in the duodenal bulb just before studies were initiated. In all instances, the ulcer was non-obstructive and no other lesion was detected elsewhere in the gastro-intestinal tract. Eight were males ranging in age from 22 to 51 years with an average of 37.6 years. The three females were 16, 32 and 38 years of age, respectively.

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† Portion of Thesis submitted by Dr. Lopusniak to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science for graduate work in Internal Medicine.

Each patient was studied in the morning after a fast of approximately 12 hours. The specially constructed double-lumen tube devised by Berk, Rehfuss and Thomas<sup>15</sup> was employed. The patient remained on a horizontal fluoroscopic table for the duration of the study, thereby permitting fluoroscopic verification of the position of the tube prior to each extraction. At the end of the fasting period a roentgenogram was obtained to record the position of the tube. This was repeated at the termination of the study, both before and after the introduction of barium through the duodenal limb of the tube to outline the cap.<sup>15</sup> Specimens were simultaneously withdrawn from the pyloric antrum and duodenal bulb through the use of a suction apparatus consisting of an electric pump with a manometric attachment. The negative pressure employed varied from 25 to 40 mm. of mercury, depending on the viscosity of the contents. Samples of approximately 5 cc. each were collected at 10 minute intervals for from 20 to 30 minutes and occasionally longer in the fasting state, and for a total of 2 hours after the feeding of the test substances.

Each test substance was studied on different days so that observations during any one morning in a given patient were restricted to one substance. After a more or less basal secretory state had been reached, each of the foodstuffs under investigation was ingested by mouth with the tube in situ. The test substances consisted of:

- (1) 120 cc. of whole milk. This was administered in the fasting state and again after one hour.
- (2) 120 cc. of a mixture (5:1) of whole milk and ordinary table cream. This likewise was administered in the fasting state and again after one hour.
- (3) A suspension of 30 gm. of casein hydrolysate ("Protolysate") and 30 gm. of a mixture of dextrans and maltose ("Dextri-Maltose No. 2") in 90 cc. of water making a total of 120 cc. of suspension. This was administered in the fasting state only and was not repeated during the two hour observation period.

The amount of each foodstuff and the frequency of administration were purposely chosen so as to duplicate clinical methods of treating ulcer which utilize these substances. The protolysate-dextri-maltose mixture represents the one recommended for general use in the dietary treatment of gastric and duodenal ulcer on the basis of the work of Co Tui and his associates.<sup>2\*</sup> Hourly feedings of milk or a mixture of milk and cream constitute the keystone of the dietary treatment of ulcer employed by our colleagues and by us at the Graduate Hospital. It is to be emphasized that we were concerned in this study with a comparison of clinical methods and not with the comparative effects of equivalent amounts and iso-osmotic concentrations of hydrolyzed and native protein.

\* Mead Johnson and Co. Brochure, January 1947.

The pH of each unfiltered gastric and duodenal sample was determined at once through the use of a Beckman pH meter which employs a glass electrode. Following filtration, the free and total acidity of each specimen were titrimetrically estimated using Toepfer's reagent and phenolphthalein as the respective color indicators.<sup>16</sup>

A total of 9 complete and 2 partial studies were obtained on 8 patients after the ingestion of protolysate-dextri-maltose. Eight complete studies were obtained on 8 patients after milk-cream. Five complete and 1 partial study were obtained on 5 patients after milk. Two patients were studied after all 3 foodstuffs. The remainder were observed after the ingestion of 2 of the 3 substances save for one patient who was available for a single study only.

## RESULTS

### *Gastric Acidity*

The plotted curve for mean pH of the gastric contents after the feeding of protolysate-dextri-maltose differed during the first hour from that for milk and milk-cream (Fig. 1). The mean pH was higher with the casein hydrolysate mixture during this period, whereas the plotted curves for all three substances closely approached each other during the second hour. In the curves obtained by computing the mean pH from the hydrogen ion concentrations, casein hydrolysate alone showed an elevation above the critical level of 3.5.<sup>17</sup> When expressed as an arithmetic mean of the pH values themselves, the duration of effective neutralization by casein hydrolysate was even longer. In contrast, milk-cream and milk were strikingly ineffective in significantly raising mean gastric pH, however computed (Fig. 1).

The effective acidity of the gastric contents was less after casein hydrolysate than after milk-cream in every sample extracted during the first 60 minutes in 5 of the 6 patients who received both preparations. In the sixth patient, the gastric pH was higher after milk-cream in the 20 minute sample. The pH values obtained from averaging the findings in all 6 patients, however, were uniformly greater during the first hour for casein hydrolysate than for milk-cream. Statistical analysis indicated, moreover, that the difference in the means was significant.

The pH of the gastric specimens remained above 3.5 for 40 minutes in more than half of the 11 patients given a single feeding of protolysate-dextri-maltose. By way of comparison, the gastric pH remained above 3.5 for 30 minutes following each milk-cream feeding in only 1 of 8 patients; at 40 minutes all 8 showed a gastric pH less than 3.5. Only 1 of 5 patients had a gastric pH in excess of 3.5 after the ingestion of plain milk; in this case the elevation persisted for only 20 minutes after the first feeding. In no patient whose gastric

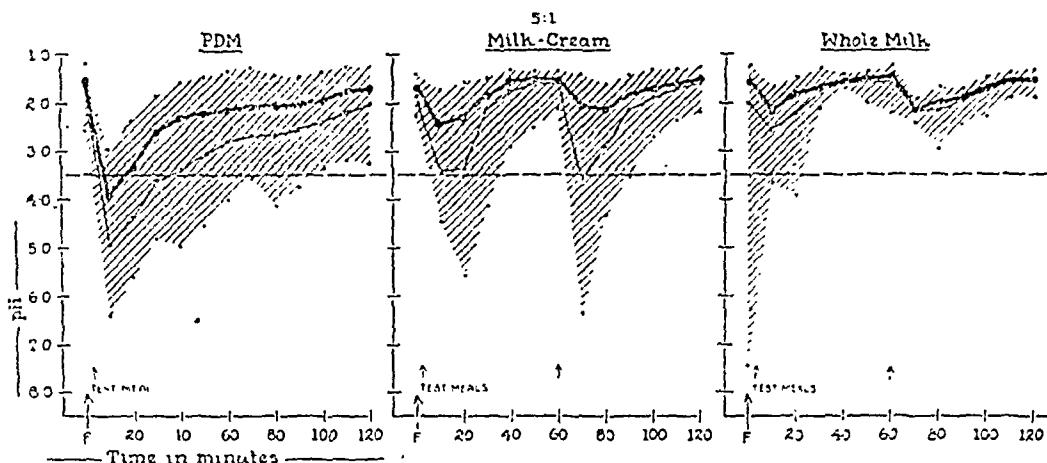


FIG. 1. The mean, maximum and minimum pH of the contents of the pars pylorica before and over a period of two hours after (1) a single feeding of protolysate-dextri-maltose (PDM); (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart. The heavier graphic line represents the arithmetic mean computed by transposing each pH reading at each time interval to its corresponding hydrogen ion concentration and then simply averaging the latter and expressing the resultant mean in terms of pH. The lighter graphic line represents the arithmetic mean calculated by simply averaging the actual pH values at each time interval.

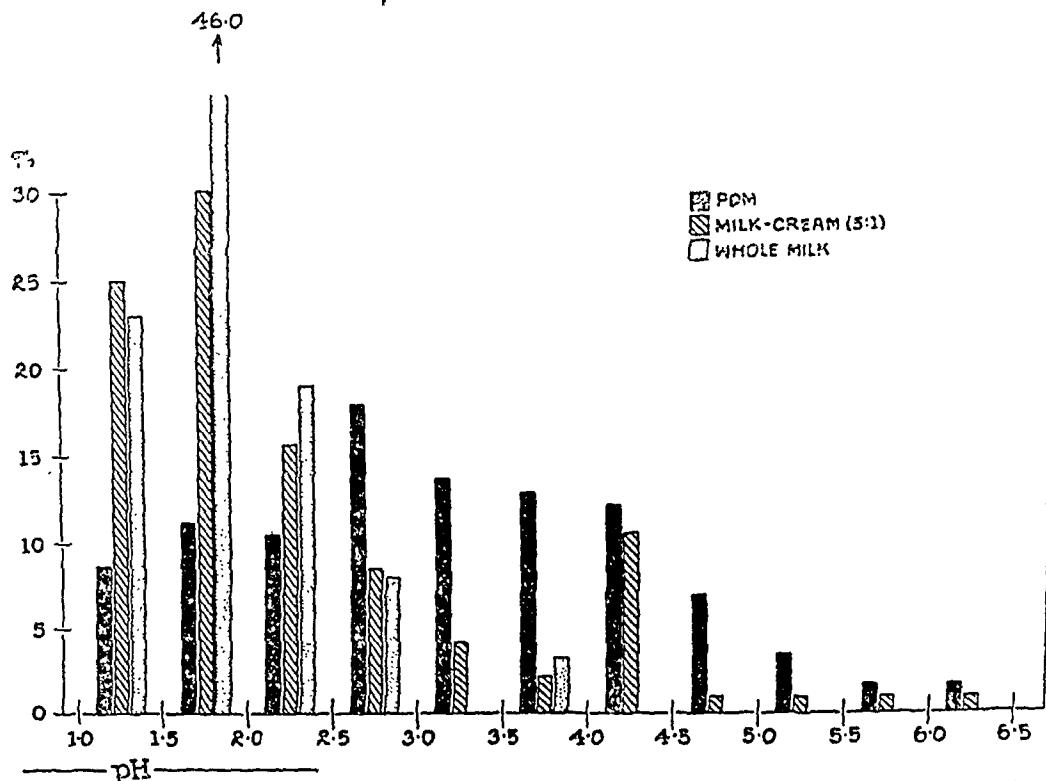


FIG. 2. The distribution of the pH values of the contents of the pars pylorica obtained at ten minute intervals over a two hour period after (1) a single feeding of protolysate-dextri-maltose (PDM); (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart.

free acid was neutralized by casein hydrolysate for 30 minutes or less, did milk-cream or milk succeed in elevating the pH above 3.5.

None of the samples obtained from the stomach after both feedings of milk had a pH in excess of 4.0 (Fig. 2). A few of the samples secured after milk-cream were in excess of pH 4.0, but the vast majority showed values less than this with most (70.8 per cent) being less than 2.5. In contrast, the pH values of the samples after casein hydrolysate were more evenly distributed with most (56.4 per cent) falling between 2.5 and 4.5. The percentage of gastric samples positive for free acid (pH less than 3.5) was definitely less after protolysate-dextri-maltose (62.8 per cent) than after milk-cream (82.3 per cent) or milk (96.8 per cent) (Fig. 3). Selection of pH 3.0 instead of 3.5 as the critical level for free acid would accentuate these differences all the more.

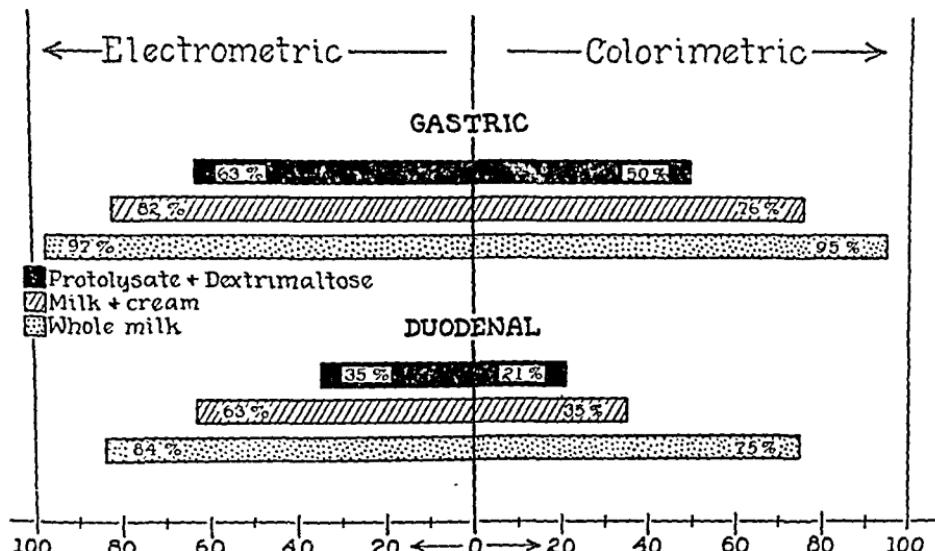


FIG. 3. The percentage of gastric and duodenal samples positive for free acid over a period of two hours after (1) a single feeding of protolysate-dextri-maltose; (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart. On the right are the comparative percentages determined by the use of Toepfer's reagent (colorimetric). On the left are the comparative percentages determined from the actual pH values (electrometric). Those samples which had a pH of less than 3.5 were considered positive for free acid.

Despite its superiority as a buffer over milk-cream and milk, the buffering of gastric acid by casein hydrolysate was decidedly imperfect in these patients. In one patient the gastric pH was never raised above 3.5. The maximum duration of neutralization of gastric free acid was 90 minutes and this occurred in only one instance. Moreover, this same subject, studied on another occasion, showed persistent neutralization of free acid in his gastric contents for only 40 minutes. The mean pH of the gastric contents calculated from the hydrogen ion concentrations, exceeded the critical level of 3.5 only in the sample extracted 10 minutes after the ingestion of the mixture; even when computed from the pH values themselves, the mean pH remained above 3.5

for only 30 minutes (Fig. 1). Had pH 3.0 instead of 3.5 been taken as the critical level for free acid, neutralization as evidenced by mean gastric pH would still have been effective for no better than 50 minutes. More than 50 per cent of the gastric specimens obtained 50 minutes after ingestion of casein

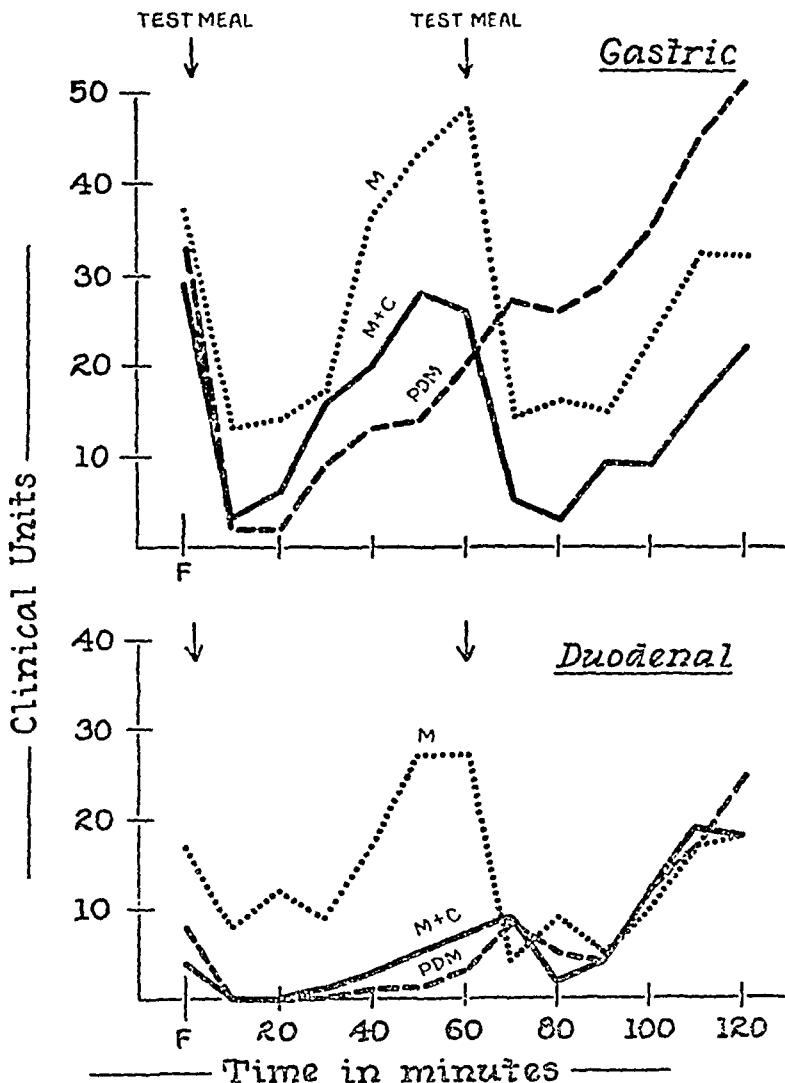


FIG. 4. The mean titrimetric free acidity of the contents of the pars pylorica and first part of the duodenum, before and over a period of two hours after (1) a single feeding of protolysate-dextromaltose (PDM); (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart. The values from which these graphs were constructed were obtained by titrating the respective samples with sodium hydroxide using Toepfer's reagent as the color indicator.

hydrolysate had a pH less than 3.5. Half of the samples (50.4 per cent) obtained during the entire 2 hour postprandial period contained free acid as indicated by Toepfer's reagent;  $\frac{2}{3}$  of these samples were within the pH range for free acid (less than 3.5) (Fig. 3).

Protolysate-dextri-maltose resulted in secondary stimulation of acid secretion in the stomach. Beginning 20 minutes after the mixture was fed, the plotted curve for mean gastric free acid showed a progressive and continuous rise (Fig. 4). This rise was particularly marked in the interval from 90 to 120 minutes after feeding, even though the mean gastric pH during this same period showed little change (Fig. 1). As judged from the plotted curve of gastric free acid, milk-cream and more especially plain milk, were also followed by secondary rises in gastric acidity. Comparison cannot be made between these preparations and casein hydrolysate, however, because the former were administered twice while the latter was fed only once during the 2 hour observation period.

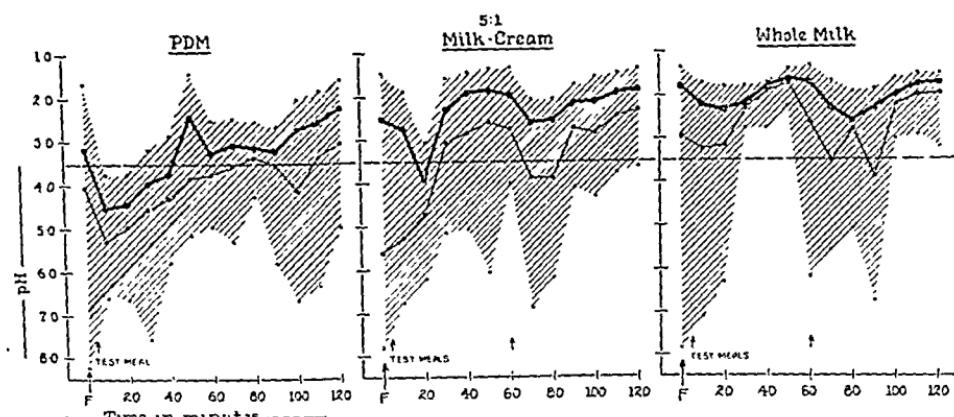


FIG. 5. The mean, maximum and minimum pH of the contents of the duodenal bulb, before and over a period of two hours after (1) a single feeding of protolysate-dextri-maltose (PDM); (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart. The heavier graphic line represents the arithmetic mean computed by transposing each pH reading at each time interval to its corresponding hydrogen ion concentration and then simply averaging the latter and expressing the resultant mean in terms of pH. The lighter graphic line represents the arithmetic mean calculated by simply averaging the actual pH values at each time interval.

#### *Duodenal Bulb Acidity*

In the first part of the duodenum the mean pH, computed by determining the arithmetic mean of the hydrogen ion concentrations, remained above the critical level for free acid (3.5) for 40 minutes after the feeding of casein hydrolysate (Fig. 5). In the case of milk-cream, the mean pH, similarly determined, exceeded 3.5 only in the sample withdrawn 20 minutes after the initial feeding. The corresponding mean pH after plain milk was still less affected; the values consistently remained below 3.0. The mean pH calculated from the pH values themselves was generally higher for each foodstuff, but especially for the protolysate-dextri-maltose mixture (Fig. 5). It should be borne in mind, however, that sharp fluctuations in reaction characteristically occur in

the contents of the first part of the duodenum of patients with an active duodenal ulcer.<sup>18</sup> The appearance, therefore, of a few high pH readings may markedly influence the arithmetic mean arrived at by simply averaging these numerical values, especially if the number of observations is not great. The influence of such extensive departures from the mode is far less when the hydrogen ion concentration corresponding to each pH reading is used as the basis for computing mean pH.

Despite the generally higher mean duodenal pH after protolysate-dextri-maltose than after milk-cream, the difference in the means at each post-prandial interval was statistically significant\* only at 30 and 40 minutes; at

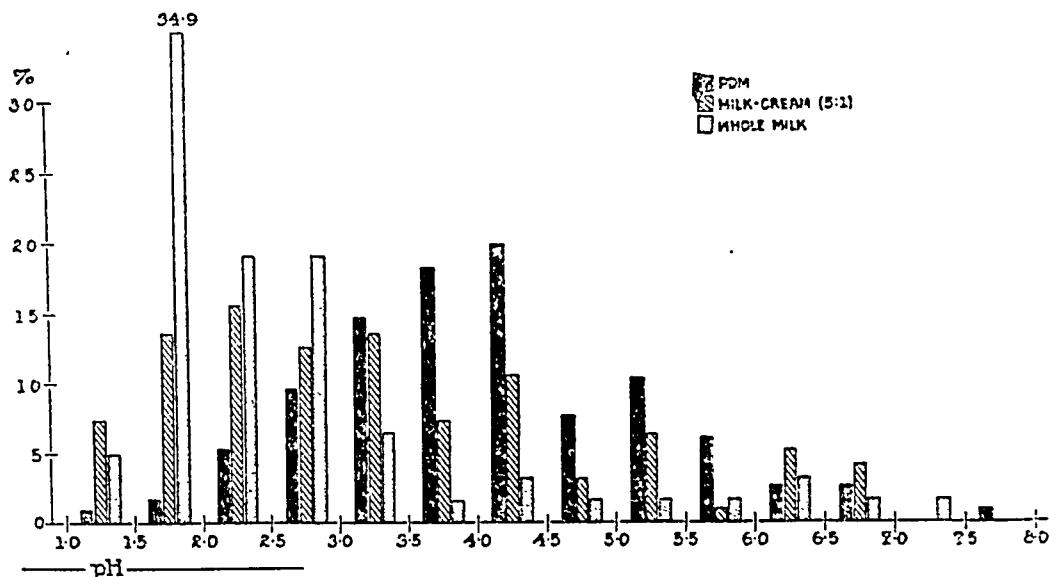


Fig. 6. The distribution of the pH values of the contents of the duodenal bulb obtained at ten minute intervals over a two hour period after (1) a single feeding of protolysate-dextri-maltose (PDM); (2) two feedings of milk-cream an hour apart; and (3) two feedings of milk an hour apart.

70 and 80 minutes the advantage actually lay with milk-cream. Of even greater import were the results in the 6 patients on whom observations were made after both substances. The difference in the means of duodenal pH in these patients was without statistical significance at each of the post-prandial intervals.

The distribution of pH values was much wider in the duodenal bulb than in the pars pylorica after all three foodstuffs (Fig. 6). Most of the pH readings following casein hydrolysate, however, tended to cluster around higher levels than was true for milk-cream and especially for milk. Furthermore, Toepfer's reagent indicated that free acid was present in 20.7 per cent of all

\* Three times the standard error.

the post-prandial duodenal samples after protolysate-dextri-maltose as compared with 35.2 per cent and 74.6 per cent after milk-cream and milk, respectively (Fig. 3). Even though a larger percentage of these samples had an actual pH within the range considered positive for free acid (less than 3.5), the percentage was still least after casein hydrolysate. Approximately one-third (34.5 per cent) of those following casein hydrolysate, two-thirds (62.5 per cent) of those following milk-cream, and five-sixths (84.1 per cent) of those following milk were within the critical pH range with respect to free acid. This discrepancy between the colorimetric and electrometric methods of estimating the presence of free acid was even more marked in the duodenal bulb than in the pars pylorica (Fig. 3). Especially was this true for the samples obtained after casein hydrolysate and milk-cream. The natural amber color of the former and the bile-staining of many of the latter apparently interfered with accurate interpretation of color changes contributed by the indicator.

The buffering action of casein hydrolysate in the duodenal bulb of these ulcer patients, in spite of its apparent advantages, was not perfect. The mean pH, computed from the hydrogen ion concentrations, remained consistently above the free acid level (3.5) for only 40 minutes (Fig. 5). Although this was prolonged to 70 minutes when the mean pH was determined by simply averaging the individual pH readings, complete neutralization of free acid (pH above 3.5) was maintained for only 20 minutes in all 8 patients. At 60 minutes, half, and at 70 minutes, more than half of the samples contained free acid (pH less than 3.5). Furthermore, approximately one-third (34.5 per cent) of all the post-prandial duodenal samples were positive for free acid as judged from their pH values. A late rise in acidity was also evidenced in the duodenal bulb after casein hydrolysate. During the final hour of the post-cibal period, the rise in mean duodenal free acid was pronounced (Fig. 4). Concomitant with this was a fall in mean duodenal pH (Fig. 5). A similar rise in duodenal free acid followed milk-cream and milk, but no valid comparisons can be made with that after casein hydrolysate for reasons previously given.

#### DISCUSSION

The popularity of milk as a basic constituent of the ulcer dietary appears to rest principally on its demonstrated ability to neutralize considerable volumes of relatively weak hydrochloric acid in vitro.<sup>19, 20</sup> In vivo, one would expect this neutralizing capacity to be augmented by gastric secretory depression resulting from the liberation of enterogastrone from the mucosa of the small intestine by the milk fat. Yet, several investigators have reported that the neutralization of gastric acid by small amounts of milk or mixtures of milk and cream fed at frequent intervals, was at best not marked.<sup>21-25</sup> The

findings reported in this study confirm and extend these observations. The hourly ingestion of 120 cc. of plain milk or milk-cream (5:1), especially the former, did not remarkably neutralize the acidity of the contents of either the pars pylorica or the duodenal bulb in patients with active duodenal ulcer.

In comparison with hourly feedings of milk and milk-cream, 120 cc. of an aqueous suspension of 30 grams of hydrolyzed protein (Protolysate) and an equal amount of carbohydrate (Dextri-Maltose No. 2) fed but once in 2 hours was more effective in neutralizing acidity in both the pars pylorica and duodenal bulb of these patients. In the duodenal bulb, however, the differences, while favoring protein hydrolysate, were of questionable significance. This would suggest that the acidity of the duodenal bulb contents is influenced by factors which tend to enhance the neutralizing effects of milk and milk-cream and to reduce those of casein hydrolysate.

One such factor is the relative amount of biliary, intestinal, and pancreatic secretion which collects in the duodenal bulb during the time the various foodstuffs are in the stomach and shortly after they begin to enter the duodenum. Thus, for example, bile-staining, often of notable degree, was evident in many of the duodenal samples after milk-cream, whereas fewer of those after milk were bile-stained and the degree of staining was not as pronounced. The presence of bile in duodenal samples obtained after casein hydrolysate was difficult to appraise because of the amber color of the protein mixture itself. Nevertheless, we were not impressed by any remarkable deepening of the natural amber color in any of the duodenal samples obtained after the ingestion of casein hydrolysate. Another factor influencing duodenal reaction is the volume as well as concentration of acid gastric juice which eventually empties into the duodenum. Unfortunately, the experimental method used in this study precluded measurement of the quantity of gastric secretion associated with each of the foodstuffs under consideration. It was observed, however, that both gastric and duodenal specimens were more readily obtained after casein hydrolysate feedings than after feedings of the other substances. Moreover, pronounced secondary stimulation of gastric secretion was noted after casein hydrolysate. Still another factor affecting the reaction in the duodenal bulb is the rapidity with which acid gastric contents enter the duodenum. Here again, unfortunately, we were unable to collect pertinent data because of the method of study. Yet, the fat contained in milk and milk-cream would be expected to cause slower gastric emptying than the fat-free casein hydrolysate mixture.

In spite of its demonstrated superiority as a buffer to both milk and milk-cream, the casein hydrolysate mixture we employed proved, under the experimental circumstances of this study, to be an imperfect neutralizer and buffer of gastric and duodenal bulb acidity in these duodenal ulcer patients. There

is reason to believe that the use of larger doses<sup>12, 13</sup>, or administration of the material hourly rather than every other hour<sup>12</sup>, would improve its antacid effects. Very likely, however, few patients would tolerate the distasteful mixture for an appreciable period of time if required to take large doses at hourly intervals. Increasing the size of the dose would also tend to invite an even larger late rise in acidity.<sup>13</sup> This assumes special importance because of the possibility of gastric and duodenal bulb acidity becoming markedly elevated during the long interdigestive period that follows the last feeding at night.

Other investigators, employing the same preparation of hydrolyzed protein we used, have reported more favorable results on gastric acidity.<sup>2, 9, 11</sup> Levy and Siler's<sup>11</sup> observations were confined to normal subjects, some of whom had no free acid in their fasting gastric contents. Yet, over half of the cases examined by them 60 minutes after the ingestion of 30 gm. of protolysate in 300 cc. of water showed a pH of less than 3.5. Even when sodium hydroxide was added to the hydrolysate solution, free acid, colorimetrically determined, appeared after 10 minutes in some subjects. Co Tui and his associates<sup>2</sup> presented data on only one ulcer patient after feedings containing 25 gm. of protolysate, a dose approximating the one employed by us (30 gm.). In that instance the gastric pH was below 3.5 within an hour after each of 3 feedings. Three of the 14 gastric and duodenal ulcer patients studied by Hodges<sup>9</sup> had no free acid in their fasting gastric contents. Moreover, he determined the presence or absence of free acid solely by colorimetric means, employing Toepfer's reagent as the indicator. Our experience would indicate that this method is not entirely reliable in the colored protolysate mixture; free acid may be considered absent when the actual pH is well within the free acid range.

Long experience on the part of many clinicians has established the value of hourly feedings of milk or mixtures of milk and cream in the treatment of ulcer. More recent experience with protein hydrolysates has also clearly indicated the beneficial clinical effects of these preparations in patients with gastroduodenal ulcer.<sup>1-10</sup> Since milk, milk-cream and casein hydrolysate were all found in this study to be without remarkable reducing effect on gastric and duodenal bulb acidity in patients with active duodenal ulcer, it would appear that either: (1) the clinical improvement following the use of these substances in the treatment of duodenal ulcer is due to more than the reduction in gastric and duodenal bulb acidity which they achieve; or (2) their effectiveness in reducing gastric and duodenal bulb acidity is greater than the current standards of measuring such effectiveness would indicate. In considering the acid problem in ulcer we have grown accustomed to thinking in terms of free acid. The latter is usually arbitrarily considered as the titratable acidity existent below pH 3.5.<sup>17</sup> The generally accepted standard for effective reduction of acidity in the stom-

ach or duodenum is neutralization of free acid or maintenance of pH above the critical level of 3.5. The justification for such a concept of the critical level of acid, particularly in the "ulcer-bearing" duodenal bulb, is open to question. When the acidity of the duodenal contents reaches certain levels, various autoregulatory mechanisms are activated which help defend the duodenal mucosa against possible harm. Thus, at pH 4.0 or below, pancreatic secretion is stimulated<sup>26</sup>; at pH 2.5 gastric motility and gastric secretion are markedly depressed, and at pH 2.0 or below, almost completely inhibited.<sup>27, 28</sup> It may be more in keeping with physiologic activity, therefore, to consider the acidity of the duodenal contents critical only when a level is reached which significantly influences gastric motility and secretion.

#### SUMMARY AND CONCLUSIONS

1. In a selected group of patients with active duodenal ulcer, a single feeding of 120 cc. of an aqueous mixture containing 30 gm. of casein hydrolysate more effectively buffered and neutralized gastric and duodenal bulb acidity over a 2 hour period than did 120 cc. of milk or a mixture of milk and cream (5:1) fed hourly over an equal period.
2. The superiority of the casein hydrolysate mixture over milk and milk-cream as a buffer and neutralizer was quite definite in the stomach, but did not appear to be significant in the first part of the duodenum.
3. Under the experimental circumstances of this study, and on the basis of the criteria used, the casein hydrolysate-carbohydrate mixture employed was an imperfect buffer and neutralizer of gastric and duodenal bulb acidity of these duodenal ulcer patients. Fairly marked secondary stimulation of acid secretion in the stomach regularly followed the feeding of this material.
4. It is suggested from the observations made in this study that: (a) the clinical improvement repeatedly observed following the use of milk, milk-cream or casein hydrolysate mixtures in patients with duodenal ulcer is due to more than the reduction in gastric and duodenal bulb acidity which these substances achieve; or (b) the effectiveness of these substances in reducing gastric and duodenal bulb acidity is greater than the current standards of measuring such effectiveness would indicate.

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PRODUCTION OF GASTRIC AND DUODENAL ULCERS BY  
THE PROLONGED ADMINISTRATION OF MECHOLYL\*

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## INTRODUCTION

In the course of experiments conducted in this laboratory, it had been observed that single injections of mecholyl in dogs produced bloody diarrhea. Post mortem examination of the stomach and intestines of these animals revealed marked hyperemia and edema of the mucosa with numerous grossly visible confluent hemorrhages and erosions in the gastric and duodenal mucosa.

To determine whether repeated daily injections of mecholyl over a prolonged period of time might lead to the production of gastric and intestinal ulcers, the following experiments were undertaken.

Mecholyl (acetyl-B-methylcholine) is a choline ester which closely resembles acetylcholine, but it is less readily destroyed by the cholinesterase and therefore has a more prolonged effect. It has been shown to have a more powerful muscarine-like action, and a less marked nicotinic-like effect than that produced by acetylcholine<sup>1</sup>. According to Gray and Ivy<sup>2</sup>, mecholyl is one of the most suitable choline esters for the stimulation of gastric secretion, being from 100 to 200 times more potent in this respect than acetylcholine when given subcutaneously. The secretion evoked by mecholyl closely resembles that produced by stimulation of the vagus nerves to the secretory cells of the stomach. More recently, it has been shown in this laboratory<sup>3</sup> that the intramuscular injections of mecholyl embedded in a beeswax-mineral oil mixture prolongs the continuous gastric secretion in approximately one-third of the dogs, and, in most of the others, the juice obtained was more acid and of greater volume than that following the subcutaneous injections of mecholyl in aqueous solution. The literature on the neuro-humoral aspects of ulcer formation has been reviewed elsewhere<sup>4</sup>.

In order to differentiate clearly between erosions and true ulcers as referred to in this discussion, an erosion may be defined as a loss in continuity of the mucous membrane, which may or may not be associated with hemorrhage. It may be superficial or deep; if it was deep, it was referred to as a crater. A true ulcer is regarded as an interruption in the continuity of the mucous membrane, but is in addition, always accompanied by an inflammatory reaction<sup>6, 7</sup>.

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## METHODS

The effects of repeated injections of mecholyl were studied in two groups of dogs. In the first group of 29 dogs, an aqueous solution of mecholyl was injected subcutaneously daily. The dosage levels were determined through experience to be the maximum each dog could tolerate without collapsing or going into shock. This 'sub-shock' dose, which was then maintained for the duration of each experiment, depended largely on the size and weight of the animal (Table 1). The daily injections were made at 9 A.M. and the animals were not fed, or given water till 4 P.M. The diet consisted of ground red beef and all animals were allowed free access to water after 4 P.M. Seven of the dogs (Table 1) were also given prostigmine along with the mecholyl. All but 1 of the dogs (dog 51—Table 1) died from the general effects of the drug.

In the second group of animals (19 dogs) the mecholyl was embedded in a beeswax-mineral oil mixture, in order to prolong the effects of the drug. The mecholyl in beeswax was prepared according to the method devised to prolong the action of histamine by Code and Varco<sup>6</sup>. The method of preparing this mixture has already been described in detail in a previous paper<sup>2</sup>. This mecholyl in beeswax preparation contained approximately 90-100 mg. of mecholyl per cc. Dosage levels were again determined through trial to be the maximum each dog could tolerate without going into shock. The mecholyl mixture was injected alternately into the shoulder and thigh muscles and the injections were given daily at 9 A.M. The diet and time of feeding were the same as for the dogs which received subcutaneous injections of mecholyl alone. There was thus a period of 7 hours after each injection when the stomach was empty. All but 4 of the dogs died from the general toxic effects of this drug; the remainder were sacrificed (Table 2).

## RESULTS

*The Effects of the Repeated Daily Subcutaneous Injections of Aqueous Mecholyl*

The experimental data are summarized in Table 1. It can be seen that following mecholyl injections, a sequence of pathological changes occurred which consisted of marked hyperemia and engorgement of the vessels, interstitial mucosal hemorrhages with superficial necrosis, erosions, and acute or subacute ulcerations in the stomach and duodenum. The dogs were injected with 10 to 50 mg. of mecholyl daily over a period of 2 to 191 days, and received a total of from 2 to 134 injections. Erosions or ulcers were found in 12 of the 29 animals studied.

In almost all instances, marked generalized parasympathetic responses accompanied every injection of mecholyl, leading to an immediate collapse and death in the first few dogs injected, especially when prostigmine was injected

TABLE 1

*Effects of the prolonged administration of mecholyl in aqueous solution*

EXP. NO.	WT.	DAILY DOSE MECHOLYL	NO. OF DOSES	TIME	RESULTS		REMARKS
					Stomach	Duodenum	
1	10	20-40	4	4	Severe hyperemia	Severe hyperemia	Died 30. min. after last dose.
2	15	40	5	7	Severe hyperemia	Severe hyperemia	Died 1 hr. after last dose. Shock.
3	9.1	10-15*	2	2	Erosions	Erosions	Died 30 min. after last dose. Shock
4	7.8	10-12*	2	2	Erosions	Hyperemia	Died 30 min. after last dose. Shock.
5	19	20*	2	2	Erosions	Mucosal Hemorrhages	Died 30 min. after last dose. Shock.
6	20	10-15	3	5	Hyperemia	Hyperemia	Died 2 hrs. after last injection. Bronchopneumonia.
7	17	10*	2	2	Mucosal hemorrages	Erosions	Died 20 min. after last dose. G-I Tract filled with blood.
8	15	10	3	5	Mucosal hemorrages	Mucosal hemorrages	Died in 30 min. after last dose.
9	17.5	10	8	10	Slight hyperemia	Slight hyperemia	Died during night.
10	17	30-40	30	40	Erosions	Erosions	Healed non-specific pancreatitis with adhesions to Liver.
11	8.6	20-30	32	44	Craters and erosions	Erosions	Stomach and intestines contained bloody fluid.
12	15.2	30-35	17	23	Mucosal hemorrages	Hyperemia	Died 7 hrs. after last dose from massive G-I hemorrhage.
13	8.1	40	6	8	Erosions	Erosions	Died from extensive G-I hemorrhage.
14	18.1	10-20	28	38	Hyperemia	Hyperemia	Peri-pancreatic and peri-gastric fat necrosis.
15	16.1	15-20	31	41	No changes	No changes	Died from infection.

TABLE 1—Continued

EXP. NO.	WT.	DAILY DOSE MECHOLYL	NO. OF DOSES	TIME	RESULTS		REMARKS
					Stomach	Duodenum	
16	15	kg. 15-20	26	days 34	Severe hyper- emia	Severe hyper- emia	Died in 30 min. after last dose. Shock
17	16.8	35	4	4	No changes	No changes	Died during the night. Bronchopneumonia.
18	20	20-30	11	12	No changes	No changes	Died during the night. Bronchopneumonia.
19	15.9	30-40	12	13	No changes	No changes	Died during the night. Bronchopneumonia.
20	14.2	20-35	41	49	Hyperemia	Hyperemia	Died 7 hrs. after the last dose from severe rectal bleeding.
21	13	15-20	52	68	Erosions	Hyperemia	Died from extensive G-I bleeding.
22	14	15-25	72	86	No change	No change	Died during the night; bilateral adrenal hemorrhage.
23	15	20-30	82	96	Erosions	Subacute ulcers	Died 20 min. after last dose. Debilitated.
24	7.7	5-10	15	10	No change	No change	Bronchopneumonia.
25	7.7	10-15	5	5	No change	No change	Died during the night.
26	18	20-40	96	104	Craters and erosions	Mucosal hem- orrhage	Died during the night. Hemorrhage into the adrenals.
27	16.8	15-30	111	120	Erosions	Mucosal hem- orrhage	Peri-duodenal fat necrosis. Died from extensive G-I bleeding.
28	20	20-30*	114	154	Subacute ulcers	Erosions	sacrificed; debilitated.
29	23.5	30-50*	134	194	Erosions	Erosions	Died of extensive G-I bleeding. No Malnutrition.

\* Received 0.25-0.5 mg. prostigmine.

together with this drug. This state of collapse was immediately relieved by the subcutaneous injection of atropine. Within 1 to 2 minutes after the mecholo-

TABLE 2

*Effects of the prolonged administration of mecholyl in beeswax-mineral oil mixture*

EXP. NO.	WT. kg.	DAILY DOSE mg.	NO. OF DOSES	TIME days	RESULTS		REMARKS
					Stomach	Duodenum	
1	14.5	80-90	3	3	Erosions	Erosions	Died 10 min. after last dose.
2	8.5	25-60	5	13	Erosions	Mucosal hemorrhages	Died during the night from G-I bleeding.
3	8.5	35-80	10	17	Erosions	Hyperemia	Died during the night from G-I bleeding
4	15.9	45-125	6	6	Erosions	Mucosal hemorrhages	Died during the night; gut filled with blood. Pneumonia.
5	15	45-125	6	6	Erosions	Hyperemia	Died during the night from extensive G-I bleeding.
6	10	20	4	4	Hyperemia	Hyperemia	Died during the night; pneumonia.
7	9	25-40	12	13	Hyperemia	Hyperemia	Died during the night from extensive G-I bleeding.
8	8	30	10	10	No change	No change	Died during the night; pulmonary thrombosis.
9	7.2	20-25	8	10	Erosions	Mucosal hemorrhages	Died during the night.
10	10.9	40-70	50	50	Erosions	Hyperemia	Died 30 min. after last dose. Debilitated.
11	10	25-55	51	51	Erosions	Hyperemia	Died during the night.
12	6.7	50-70	2	2	Severe hyperemia	Hyperemia	Died from massive G-I bleeding.
13	6.7	35-50	7	7	Severe hyperemia	Hyperemia	Died from massive G-I bleeding.
14	14	30-50	37	37	Hyperemia	Hyperemia	Died 2 hours after last dose fat necrosis in peri-duodenal fat.
15	5.9	10-35	71	73	Severe hyperemia	Hyperemia	Died 1 hour after last dose.

TABLE 2—Continued

EXP. NO.	WT.	DAILY DOSE	NO. OF DOSES	TIME	RESULTS		REMARKS
					Stomach	Duodenum	
16	7	30-90	68	74	No changes	No changes	Sacrificed.
17	6.5	30-70	20	20	No changes	No changes	Sacrificed.
18	8.5	80-90	5	5	Mucosal hemorrhages	Hyperemia	Sacrificed 1 hr. after last dose. Profuse rectal bleeding.
19	9.5	80-90	5	5	Mucosal hemorrhages	Hyperemia	Sacrificed 1 hr. after last dose. Profuse rectal bleeding.

lyl was given, sweating, panting, salivation, lachrymation, retching and excessive vomiting were noted.

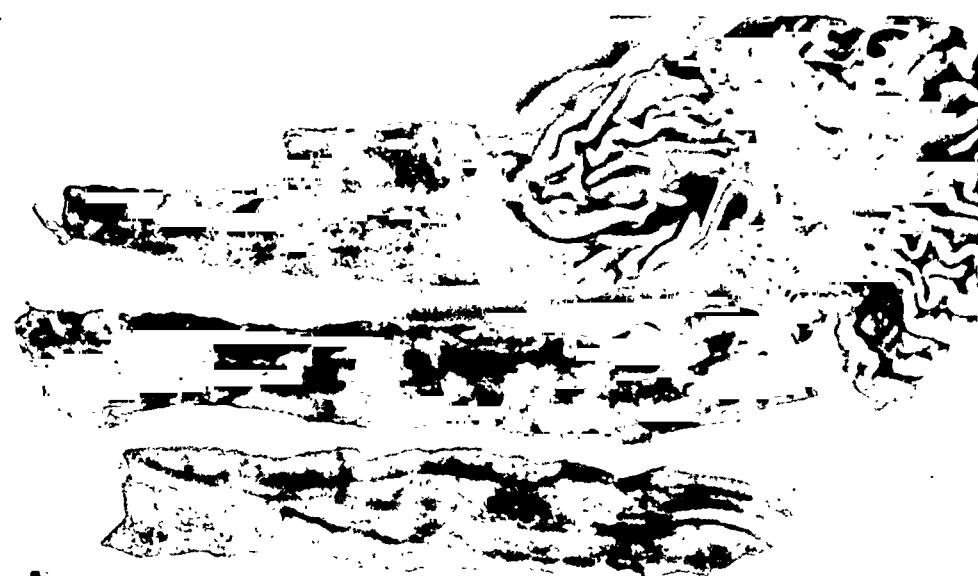
The vomitus was frequently blood-tinged and occasionally massive hematemesis occurred. Mecholyl also stimulated the contractions of the urinary bladder and caused increased gastro intestinal motility which resulted in immediate urination and defecation. The stools were well formed at first and of normal color and consistency, but within 10 to 15 minutes, subsequent bowel movements were looser and blood-tinged and eventually watery, mucoid and bloody diarrhea developed of the type commonly seen in human cases of acute ulcerative colitis.

The bloody diarrhea usually terminated in most dogs within 1-2 hours after injection, and within 8 to 24 hours the stools again became formed and were of normal consistency, but tarry in color. In numerous instances (Expts. 11, 12, 13, 20, 21, 25, 27, 29, Table 1) (after repeated injections), the dogs continued to have frequent bloody stools and rectal bleeding which continued for 12 to 18 hours after injection and finally such animals died from the extensive hemorrhages from the gastro intestinal tract. On post mortem examination of such dogs, the stomach and intestines were filled with varying amounts of blood and the gross appearance of the gut in most instances was similar to that seen in Figs. 1A and B.

The stomach was usually diffusely hyperemic, and revealed multiple mucosal hemorrhages, focal areas of superficial necrosis, and erosions. This hyperemic discoloration of the stomach was most severe in the fundic portion, which was sharply demarcated from the paler pyloric region as seen in Figs. 1A and B. Beginning sharply at the most proximal end of the duodenum, the hemorrhagic involvement of the mucosa extended throughout the entire intestine with decreasing severity as the ileum was approached (Figs. 1A and B).

The severity of the hemorrhagic changes and superficial necrosis observed

at autopsy depended mainly on the time interval between the last injection and the time of death. In most instances the mucosal alterations of the stomach



A



B

FIG. 1

A (upper) and B (lower), severe and extensive hyperemia of the gastro-intestinal mucosa with multiple small mucosal hemorrhages and focal necrosis, in dogs #28 and #17, following the injections of mecholyl. Note that the hemorrhagic appearance is more extensive in B.

and small intestine were most pronounced when death ensued within 3 hours after the last dose of mecholyl. In those animals which were found dead 12-18 hours after the last injection, no changes or only slight hyperemia could be

demonstrated in these regions (Table 2, Expts. 10, 17, 18, 19, 22, 24). Similar mucosal changes were observed in the large bowel of these animals and will be the subject of a subsequent publication.

Histological examination of the hemorrhagic portions of the stomach and duodenum showed marked dilation of blood vessels, especially capillaries and the presence of acute, diffuse interstitial hemorrhage into the mucous membrane with necrosis of the most superficial layers of the mucosa (Fig. 2). In a number of situations, underlying a relatively intact mucous membrane, in which

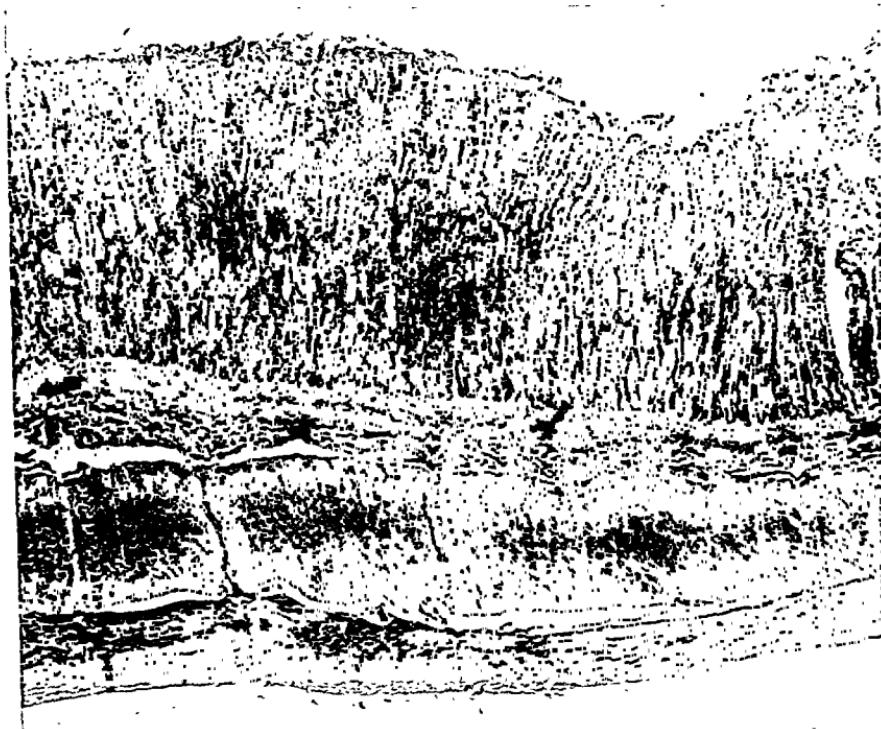


FIG. 2

Showing interstitial hemorrhage into outer two-thirds of mucous membrane and superficial necrosis of outer third of the mucosa.  $\times 35$ .

interstitial hemorrhage had occurred, focal infiltration by acute inflammatory cells was noted, suggesting a focal hemorrhagic gastritis or duodenitis.

The erosions were multiple and were usually confined to the fundic portion of the stomach and were less often seen in the pylorus and duodenum. Multiple sections taken through the erosions seen in the gross revealed varying degrees of hemorrhage and necrosis of the mucous membrane, but the basal layers of the mucosa were intact (Fig. 3A). In several instances, the necrotic tissue was infiltrated by polymorphonuclear leucocytes (Fig. 3B). In dog

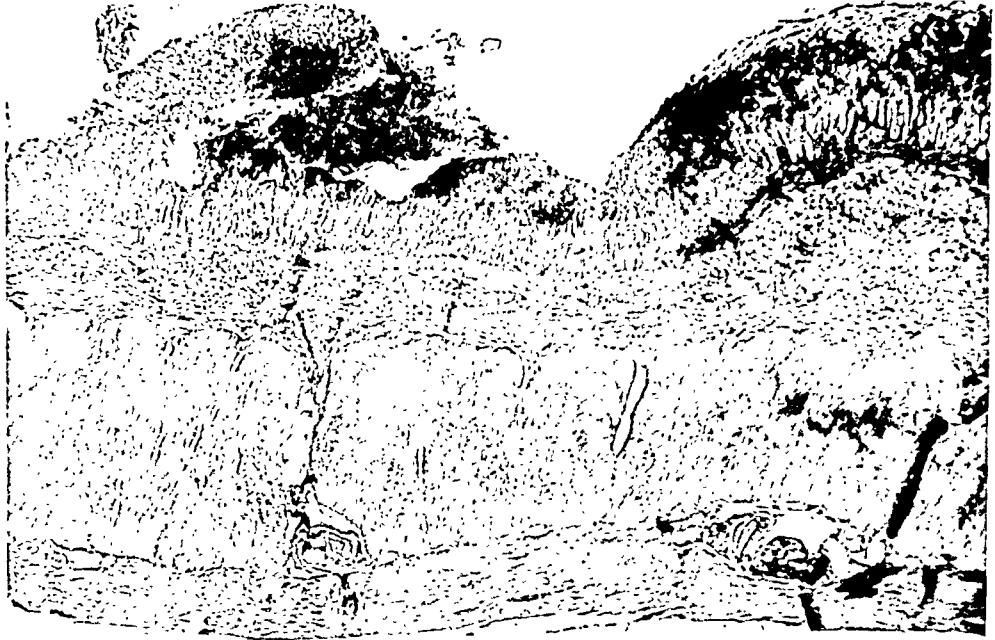


FIG. 3A

Superficial gastric erosion of the outer two-thirds of the mucosa, which is the seat of hemorrhage and necrosis (dog #15). Note that the basilar layers of the mucous membrane are intact.  $\times 23$ .



FIG. 3B

Higher power of deep erosions seen in section 3A, showing the remaining inner third of the gastric mucosa. Note that the necrotic tissue is infiltrated by polymorphonuclear leucocytes, but that there is a sparse number of inflammatory cells in the muscularis mucosae.  $\times 84$ .

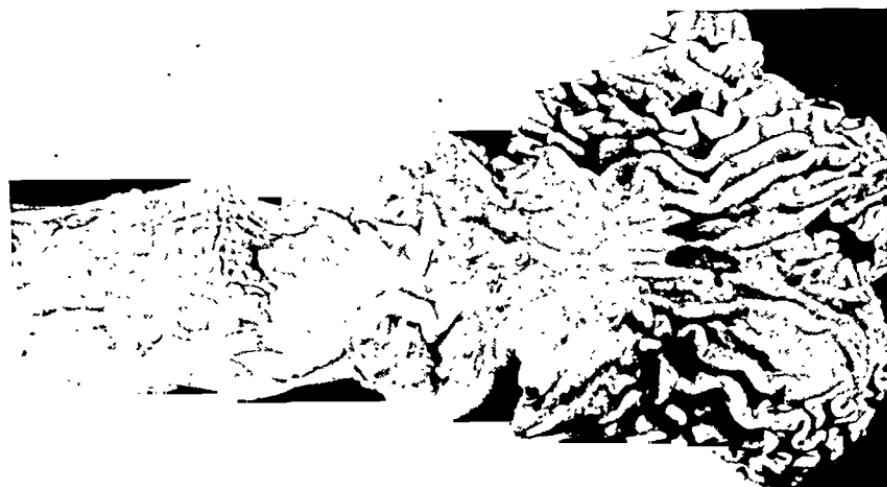


FIG. 4A

Twin gastric craters, and multiple scattered superficial erosions in dog #37 after repeated injections of mecholyl. Note the resemblance of these lesions to true ulcers.

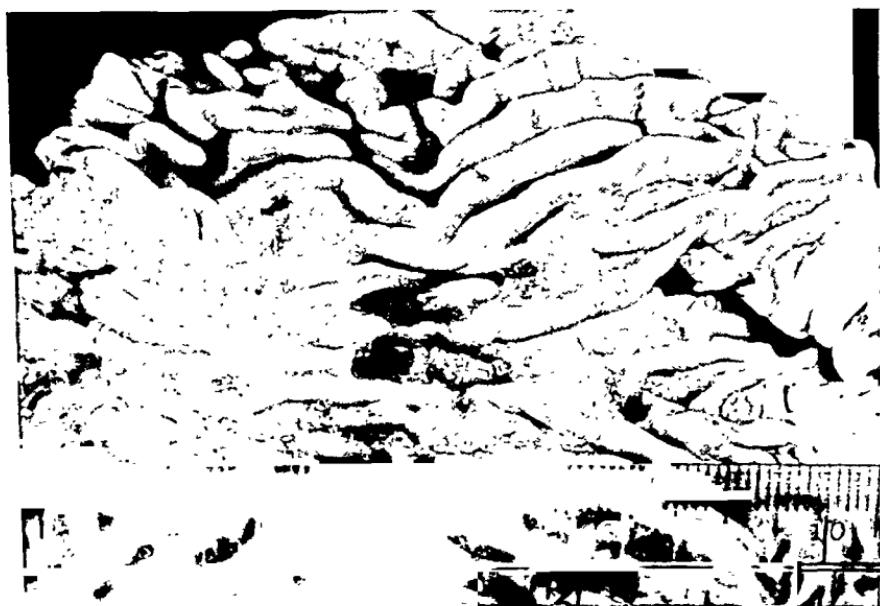


FIG. 4B

Closer view of the craters seen in Fig. 4A, showing remnants of fresh clotted blood in their bases.

37 (Table 1, Exp. 11) twin gastric lesions were noted which, in the gross (Figs. 4A and B) resembled true ulcers. Microscopic examination however, (Fig. 5)

showed them to be deep craters or erosions which consisted of a bland necrosis of the mucosa in which no inflammatory exudate was present.

Acute or subacute gastric or duodenal ulcers were encountered in 2 animals. Two duodenal ulcers were found in the proximal portion of the duodenum of dog 39 (Table 1, Exp. 23) after 82 daily mecholyl injections, during a period of 96 days (Fig. 6A and B).

Terminally, this dog was in a debilitated conditions and died from extensive gastro intestinal hemorrhages, 18 hours after the last injection. Microscopic examination of the duodenal lesions showed them to be subacute penetrating

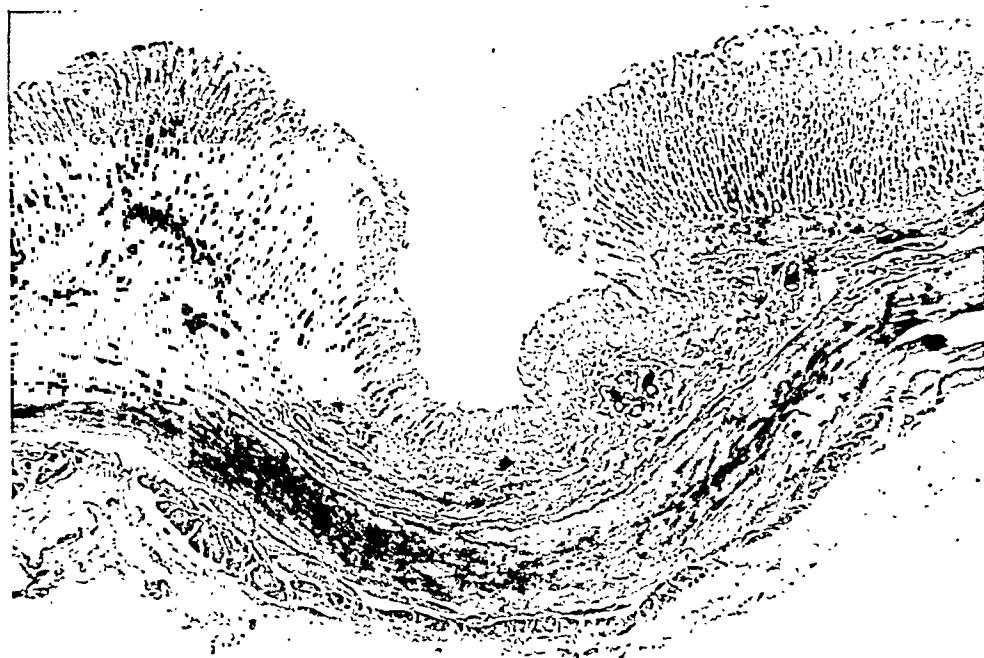


FIG. 5

Microphotograph of gastric craters seen in Fig. 4, showing the deep erosions, which in the gross could be mistaken for true ulcers. Note that residual mucosal glands still remain and that no inflammatory exudate is present in mucosa or submucosa.  $\times 23$ .

ulcers with overhanging edges and a necrotic inflammatory base. The blood vessels were hyperemic and the inflammatory exudate extended deeply into the submucosa (Fig. 7A and 7B).

Multiple gastric ulcers in the pyloric region of the stomach together with numerous erosions in the fundus were found in dog 51 (Table 1—Exp. 28) following 114 injections of mecholyl (Fig. 8A and B). Prostigmine in 0.5 mg. doses had been given with the last 10 mecholyl injections. This dog, which had lost much weight and was sacrificed when in a debilitated condition, showed the presence of multiple acute and subacute gastric ulcers. Fig. 10A and B show

an acute superficial gastric ulcer, the base of which was infiltrated by polymorphonuclear leucocytes. The muscularis mucosa was necrotic and the



FIG. 6

A (upper) and B (lower)—Two duodenal ulcers and multiple gastric erosions in dog #39 after 82 mecholyl injections. Note the hemorrhagic appearance of the gastric and duodenal mucosa.  
B—Close up view of the duodenal ulcers showing the over-hanging edges.  $\times 23$ .

adjacent submucosa was also infiltrated by acute inflammatory cells. In this same animal, a definite subacute gastric ulcer with terraced edges, penetrating



FIG. 7A

Photomicrograph of lesions seen in Fig. 6, showing the large penetrating subacute duodenal ulcer extending through the muscularis mucosa into the submucosa and superficially, at the left, into the muscularis. Note the over-hanging edges.  $\times 20$ .

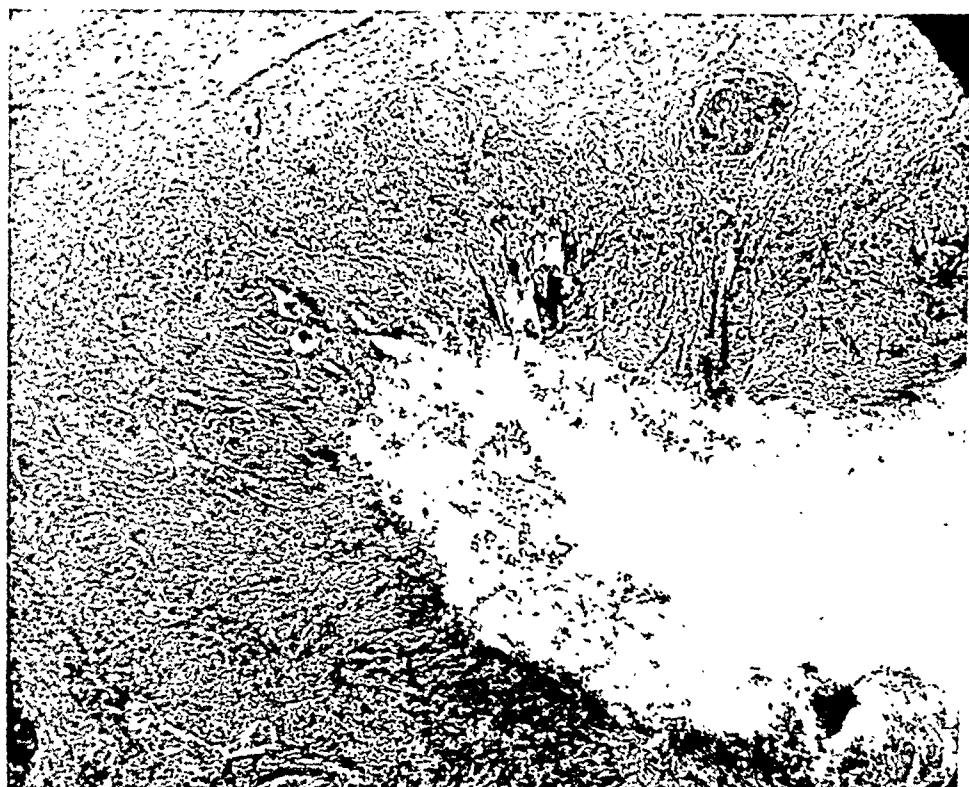


FIG. 7B

Higher power view of the base of the subacute duodenal ulcer seen in Fig. 7A, showing the overhanging edge and the inflammatory exudate deep in the submucosa. Note the hyperemia of the vessel at the left, in the submucosa.  $\times 101$ .

to the submucosa was present (Fig. 9A and B). The inflammatory process, (polymorphonuclear leucocytic and lymphocytic infiltration) had extended into the submucosa.

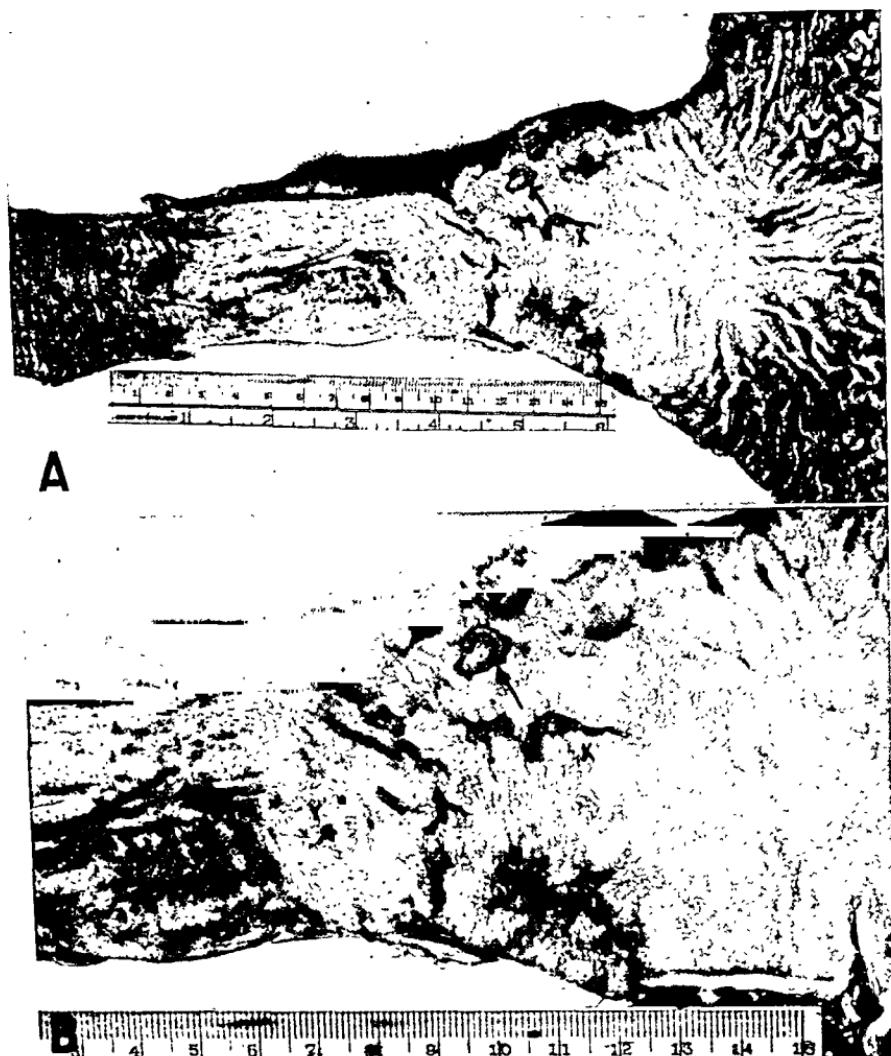


FIG. 8

A (upper). Multiple gastric ulcers in the pyloric portion of stomach and numerous gastric and duodenal erosions. Note the hemorrhagic appearance of the fundic portion of the stomach.

B (lower). Closer view of the same lesions, showing the punched-out appearance of some of the larger gastric ulcers.

It is interesting to note that although many of the dogs died from extensive gastro intestinal hemorrhages, most of the animals died from the general effects of the drug.



FIG. 10A

Microphotograph of gastric lesion indicated by X in Fig. 8, showing an early acute gastric ulcer.  
 $\times 21$ .

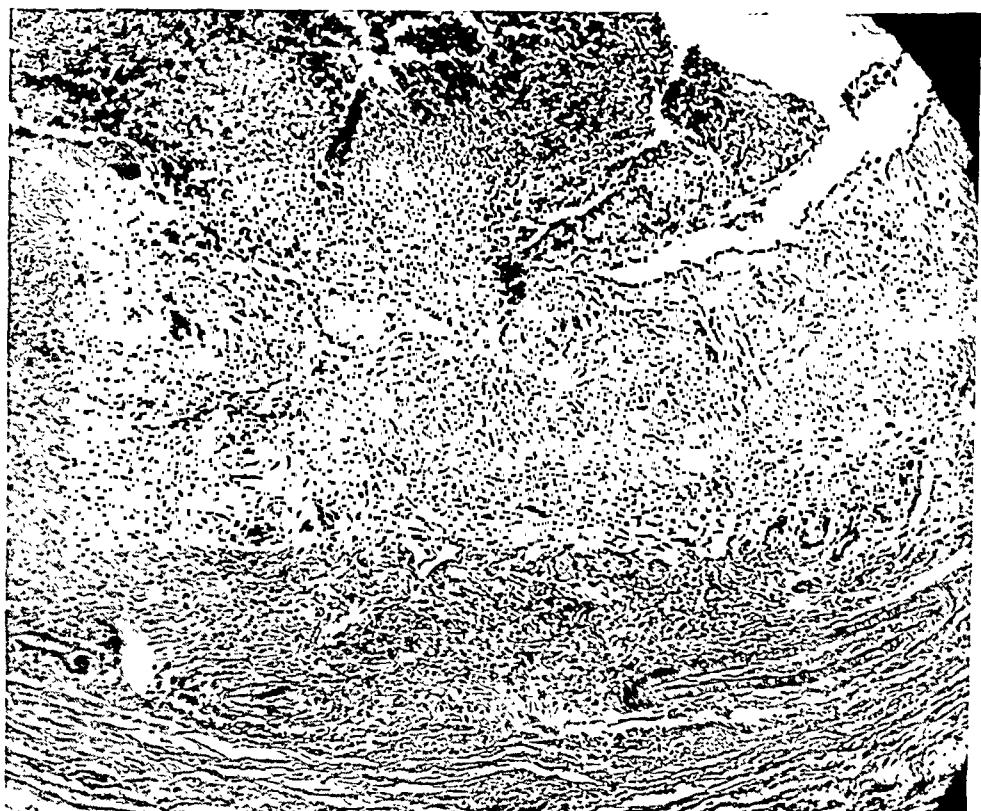


FIG. 10B

Higher power view of the base of the acute ulcer in Fig. 10A, showing complete loss of mucosa and infiltration of the submucosa and muscularis by inflammatory cells.  $\times 101$ .

and the gross and microscopic changes were essentially similar, although no genuine gastric or duodenal ulcers were encountered in this group. Other lesions in the intestinal tract were, however, produced which will be reported subsequently.

Here again, the death of 7 of the 19 dogs could be attributed to profuse gastro intestinal hemorrhage, of the remainder 4 were sacrificed and the others died of the general toxic effects of the drug.

#### DISCUSSION

The experiments reported demonstrate that repeated injection of mecholyl may produce a sequence of pathological changes ranging from interstitial mucosal hemorrhage, through erosion to true ulcer formation. The most striking feature of these observations has been the hemorrhagic appearance of the gut noted at autopsy (Fig. 1).

The microscopic findings in the numerous sections taken from the gastro intestinal tract strongly suggests that vasodilatory action of mecholyl on blood vessels was the main factor in the pathogenesis of these lesions. From the gross and histological character of the lesions encountered in this study, the probable sequence of pathological events appears to be as follows: The marked vascular engorgement and hyperemia gave rise to stasis, increased capillary permeability and tissue anoxia, which resulted in extravasations of red blood cells into the mucosa, and was followed by superficial necrosis of the mucous membrane, erosions and eventually led to the formation of true ulcers.

Additional factors, such as trauma, acidity and malnutrition, probably play a part in the genesis of the lesions observed in these experiments. Wolf and Wolff<sup>8</sup> have demonstrated that erosions in man may be induced by trauma incident to vigorous gastric contractions in engorged, friable mucous membranes. In our animals, marked gastric contractions were evidenced by frequent vomiting immediately following mecholyl injections. The role of acidity per se does not appear to be the initiating factor of these lesions. Although it has been shown that mecholyl in beeswax can prolong the secretion of a highly acid juice in some animals<sup>9</sup>, gastric or duodenal ulcers did not develop in the group of dogs which had received repeated injections of mecholyl in beeswax. However, after prolonged and repeated administration of mecholyl, the resistance and regenerative powers of anoxic mucosa may diminish to a point where it becomes more susceptible to the digestive action of the acid-pepsin content of the gastric juice. The acid therefore appears not to be of prime importance in the initiation of the erosions and ulcers, but may have delayed the healing or caused the spreading of mucosal lesions produced by the vascular disturbances<sup>9</sup>.

The dogs in which gastric or duodenal ulcers were found, were terminally in

a poorly nourished state. Several dogs which had received a similar number of mecholyl injections, but were better preserved physically, did not develop ulcers. These observations are in agreement with those of others<sup>10-13</sup>, who have called attention to the importance of malnutrition in the development of experimental ulcers. It has also been suggested that dietary deficiencies and malnutrition may be important in the initiation and persistence of peptic ulcers in man<sup>14-16</sup>.

The results of the present study with mecholyl have demonstrated the importance of repeated profound circulatory disturbances as the main factor in the initiation of acute gastro intestinal lesions, and therefore reinforce the concept of vascular changes as the basis of peptic ulcer formation.

#### CONCLUSIONS

1. It has been shown that hemorrhages, erosions and acute and subacute gastric or duodenal ulcers can be produced in dogs by the prolonged daily administration of mecholyl.
2. Vascular stasis, altered capillary permeability, hemorrhage, tissue anoxia and necrosis of mucosa are suggested as the sequence of events in the pathogenesis of these lesions and additional factors such as trauma, acidity and nutritional state have been discussed.
3. These experiments reenforce the vascular concept of peptic ulcer formation.

Acknowledgements are made to Merck & Company for supplying the Mecholyl; and to Hoffmann-La Roche for supplying Prostigmine.

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## THE EFFECT OF MECHOLYL IN BEESWAX ON GASTRIC SECRETION\*

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### INTRODUCTION

Earlier studies on the effects of acetyl-B-methylcholine (mecholyl) have shown that the administration of small doses of mecholyl subcutaneously caused an increase in the volume and acidity of the gastric secretion.<sup>1-5</sup> Following the injection of larger doses of this drug, the juice obtained was scanty, mucoid, of low acidity or alkaline in character.<sup>2, 3, 4, 7, 8, 9</sup> Gray and Ivy<sup>2</sup> noted that the continuous acid gastric secretion produced by repeated small doses of mecholyl after reaching a maximum, declined in spite of the continued injections, indicating that the secretory mechanism had become refractory to the drug. This was recently confirmed by others.<sup>5</sup> Stavraky<sup>4</sup> demonstrated that mecholyl was a strong stimulant for the secretion of pepsin. The administration of mecholyl by iontophoresis resulted in an alkaline mucoid gastric secretion.<sup>10</sup> Following the oral administration of acetyl-B-methylbromide in doses of 100 to 600 mg., in man, Wolf and Wolff<sup>6</sup> reported on increased acid secretion which became maximum in 30-45 minutes after the injection of the drug and then the acid output quickly fell to its control level.

In the present series of experiments, in an attempt to obtain a prolonged and continuous action, the mecholyl was embedded in a beeswax-mineral oil mixture, according to the method devised by Code and Varco<sup>11</sup> for prolonging the action of histamine. Since mecholyl had not been administered in beeswax before, this study was undertaken to determine the effects of this mixture upon gastric secretion as compared to those obtained with large single doses of mecholyl in aqueous solution injected subcutaneously.

### METHODS

A total of 23 experiments were performed on 21 dogs which weighed 6 to 35 kg. Three of the experiments were carried out on a dog with a permanent gastric fistula; the remainder were acute experiments on dogs which had been specially prepared. For the acute experiments, 20 dogs under nembutal anaesthesia (25 mg. per kg.) or under a mixture of chloralose and urethane (1:10 dissolved in 60 cc. of saline and given 3 cc. per kg.) were used in which the esophagus and pylorus were ligated and a metal fistula was inserted into the

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most dependent portion of the stomach. The dogs were fasted for at least 18 hours prior to the experiment to be sure that the stomach was empty at the onset of the experiment.

In every instance the fasting secretion, if any, was collected for 30 minutes prior to the injection of mecholyl. The pH of the gastric secretions before and after the administration of the drug was determined on the Beckman pH meter. Two different preparations of mecholyl were employed and each was administered by a different route.

*Subcutaneous Injection of Mecholyl in Aqueous Solution.* One gram of dry powdered mecholyl chloride (Merck & Co.) was dissolved in 100 cc. of distilled water or saline, resulting in a concentration of 10 mg. per cc. The mecholyl was then given by subcutaneous injection in doses which varied from 15 to 35 mg. The size of the dose was determined through experience to be the maximum the animal could tolerate without going into shock or state of collapse. This 'sub-shock' dose depended partly on the size and the weight of each dog. These dosage levels were generally much higher than that used by previous investigators. The gastric secretions were collected every 15 to 30 minutes at the start of each experiment and later at half-hourly or hourly intervals.

The effects of the subcutaneous injections of mecholyl were studied on 4 dogs under anesthesia and on one with a permanent gastric fistula. The dogs in this series weighed 6 to 20 kg. In several experiments, the same dose of mecholyl or 2 doses of histamine (0.5 mg.) 10 minutes apart, were injected subcutaneously into dogs when the initial mecholyl secretion had declined.

*The Injection of Mecholyl in Beeswax-Mineral Oil Mixture.* The mecholyl in beeswax mixture was prepared in small quantities using 1 gram of mecholyl chloride (Merck & Co.) to 8 cc. of 4.8 per cent beeswax in mineral oil mixture (supplied by Ayerst, McKenna Harrison). Special care was taken to see that the mecholyl was kept dry since it was very hygroscopic. The mecholyl was finely ground in a mortar and to it was added 8 cc. of the molten 4.8 per cent beeswax-mineral oil mixture. The contents of the mortar were again mixed until the mixture was homogenous. The molten preparation was then drawn into 1 cc. tuberculin syringes and when the mixture cooled to room temperature, the semi-solid mass was injected through 18 gauge needles. The mixture of mecholyl in beeswax thus obtained contained approximately 90-100 mg/l of mecholyl chloride per cc.

This mixture was then injected intramuscularly in doses which varied from 0.2 to 2.0 cc. with dogs weighing 7 to 35 kg. Here again the size of the dose was the maximum the dog could tolerate or the 'sub-shock' dose. The gastric secretions were collected at 15 to 30 minute periods at the start of each experiment and later at 30 to 60 minute intervals.

## RESULTS

*The Effect of Subcutaneous Injection of Mecholyl.* The typical responses obtained following a single subcutaneous injection of mecholyl (in aqueous solution) are illustrated in Figs. 1 and 2. It can be seen that following the administration of large doses of this drug a rapid secretory effect was obtained which was accompanied by the immediate onset of salivation, lachrymation and increased gastrointesinal motility. The secretory response reached its maximum within the first half hour and then declined rapidly, lasting a total of 45 to 90 minutes. This juice was mucoid in consistency and of low acidity (pH 4.25-6.66). In the acute experiments the volume of the gastric secretion

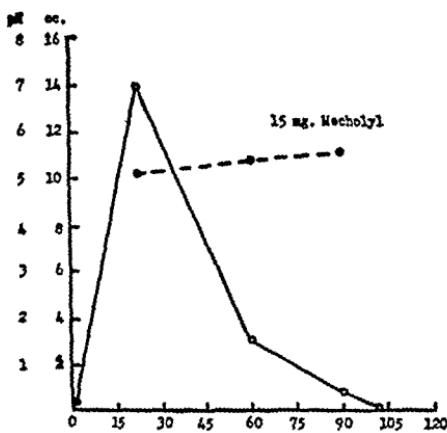


FIG. 1

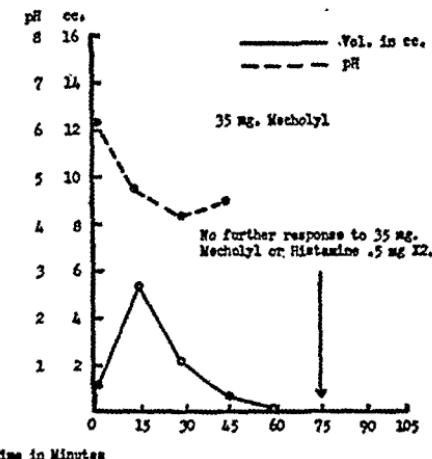


FIG. 2

FIGS. 1 AND 2. The gastric secretory response to single injections of mecholyl in aqueous solution in dogs 12 (10 kg.) and 17 (15 kg.) respectively. Note the immediate response, rapid decline and the low acidity of the juice obtained.

varied from 2 cc. to 17 cc. per hour. A similar response to mecholyl was obtained in a dog with a chronic gastric fistula, but the swallowed saliva and the regurgitation of bile interfered with the accurate determination of the results.

In 1 dog, the injection of a similar dose of mecholyl after the response to the initial dose had declined, failed to elicit an additional secretory response, and subsequent injections of histamine were also without effect. Another animal was found to be completely refractory to the initial dose of mecholyl and to repeated injections of histamine.

*The Effect of Mecholyl in Beeswax.* Figs. 3 and 4 illustrate the type of secretory response evoked by the single intramuscular injections of mecholyl

in beeswax. The gastric secretion obtained in 12 out of 18 dogs following the administration of mecholyl in beeswax-mineral oil mixture was of greater volume and higher acidity than that observed after the injection of mecholyl in aqueous solution, and in 6 of the animals the secretion was definitely prolonged (Figs. 3 and 4).

In the remaining 6 dogs no response or a scanty mucoid alkaline secretion was noted after the implantation of the mecholyl in beeswax. Although the amounts of mecholyl injected with the beeswax (20-200 mg.) were in most instances greater than the lethal subcutaneous dose for these animals, being

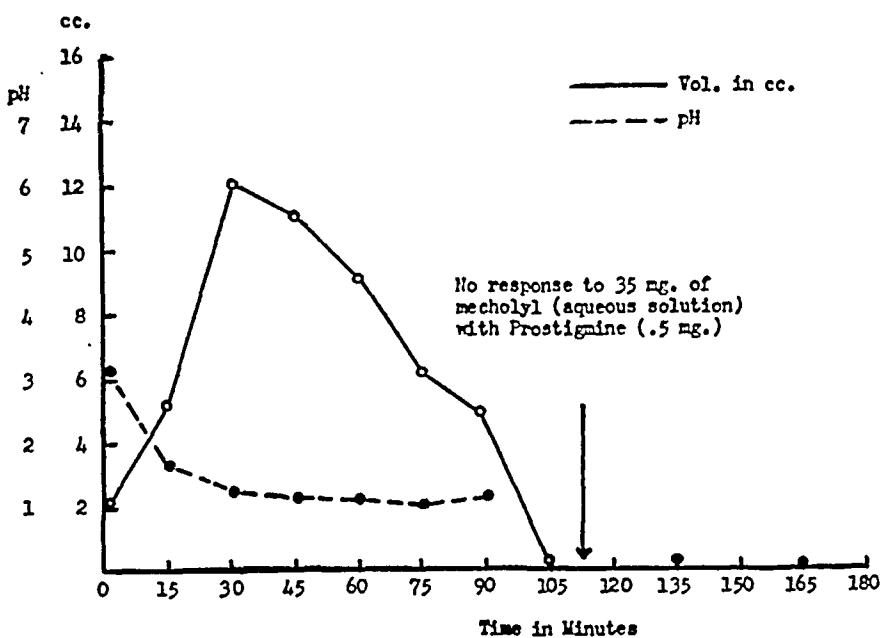


FIG. 3. The secretory response to 0.7 cc. or (approximately 60 mg.) of mecholyl in beeswax in dog 1 (12 kg.). Note the continuous secretion and the high acidity of the juice obtained; no further response to 35 mg. of mecholyl (aqueous solution), with prostigmine 0.5 mg.  $\times 2$ .

from 2 to 4 times greater than that given by the subcutaneous injections of the aqueous solution of mecholyl, no untoward effects were noticed. In all instances, the salivation, lachrymation and the increased gastrointestinal motility commenced 2 to 5 minutes following the injections and lasted longer than the gastric secretory response. The general effects to mecholyl were also observed in the dogs in which no gastric secretion was obtained, indicating that the implantation of the mecholyl in beeswax definitely prolonged the mecholyl effect in all the experiments, even in the absence of a secretory response.

In dogs in which a gastric secretion was obtained, it usually commenced 5-10 minutes after the injection, reached its maximum in 15-30 minutes and lasted 30 minutes to 6 hours. In only 6 dogs did the secretion last from  $1\frac{1}{2}$  to 6 hours

(Figs. 3 and 4) and in the remainder, the secretory response declined rapidly in 30 to 60 minutes. The juice obtained was watery to mucoid in character of very high acidity (pH 1.0-3.5) and clearly resembled that seen after vagal stimulation (Figs. 3 and 4). In the acute experiments the volume of gastric secretion during the first hour varied from 14 to 37.0 cc. (Figs. 3 and 4). In the chronic fistula dog, a more copious secretion was obtained in the first hour, which was partly due to the swallowed excess saliva, although the pH varied from 1.28 to 1.80.

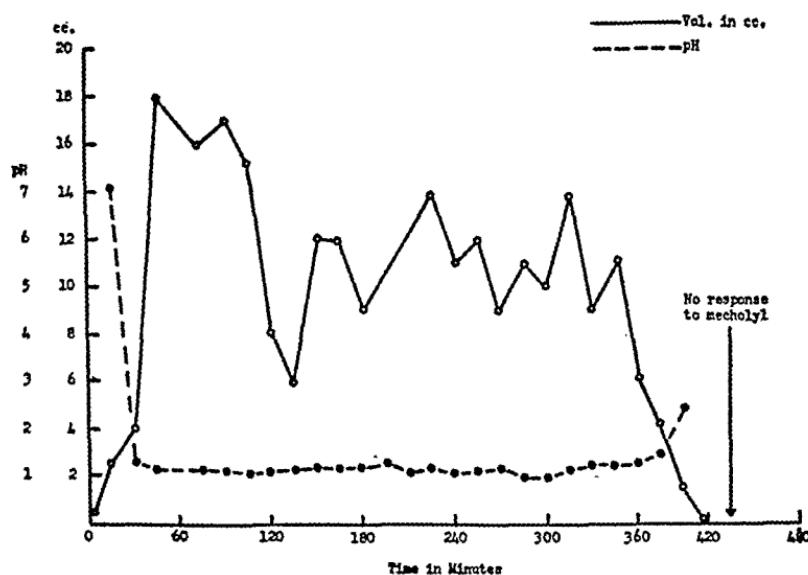


FIG. 4. Effect of 75 mg. mecholyl in beeswax in dog 10 (15 kg.), under nembutal anaesthesia. Note that the gastric secretion was continuous for 6½ hours and of very high acidity. No further response to same dose of mecholyl when initial secretion had declined.

When the mecholyl secretion had declined, the second injection of a similar dose of mecholyl in beeswax produced no further effects in 4 of the dogs (Figs. 3 and 4), and in 2 of these the further addition of prostigmine (0.5 mg.), 10 minutes later also failed to elicit a secretory response (Fig. 3) although an increase in salivation was noticed.

When a second dose of mecholyl in beeswax was given the 3 dogs which showed no secretion following the first injection of mecholyl mixture, no effect was obtained. Two of these animals were also refractory to histamine injections, while a profuse watery highly acid secretion was obtained in the third following the histamine injection.

The 3 dogs in which a scanty alkaline secretion was obtained following the mecholyl injection, were also refractory to subsequent doses of mecholyl or his-

tamine. The responses to the mecholyl in all these experiments were not directly related to the size of the doses injected.

#### DISCUSSION

These experiments demonstrate that the injection of large single doses of mecholyl in aqueous solution or embedded in beeswax can stimulate an acid secretion in most of the dogs and that the administration of the mecholyl in beeswax can prolong the secretory response in at least one third of the animals tested.

The type of gastric secretion observed after single large doses of mecholyl in aqueous solution was in close agreement with the findings of other<sup>4, 5, 6</sup> (Figs. 1 and 2) although the doses used in this investigation were generally much larger than those used by previous workers. The volume and the acidity of the juice provoked by the mecholyl in beeswax was definitely greater than that noted after the injection of the mecholyl alone, and was very similar to the type of secretion obtained by Gray and Ivy<sup>2</sup> and others<sup>3, 5</sup>, with repeated stimulation of small doses of mecholyl, indicating that the mecholyl suspended in the beeswax was being slowly absorbed (Figs. 3 and 4). The watery mucoid character and the extremely high acidity of this secretion closely resembled that obtained by stimulation of the vagi in dogs.<sup>12</sup>

The failure to obtain a second response with the same dose of mecholyl (either in aqueous solution or in the beeswax) or to histamine (Figs. 2, 3, 4), suggests that the secretory apparatus has become refractory not only to mecholyl, as previously shown by Gray and Ivy<sup>2</sup> and others<sup>5</sup>, but to histamine as well. Although the exact reason for this refractory state after mecholyl is not definitely known, it may be due to the severe hyperemia, congestion and edema of the hemorrhagic gastric mucous membrane so frequently seen when the stomach was examined, both grossly and microscopically, after a single large dose of mecholyl.

In spite of the limited number of dogs used in this study, 4 or approximately 20 per cent of the series were completely refractory to mecholyl, while another 4 dogs or 20 per cent responded with a scanty alkaline secretion. Nearly all of these 8 dogs were also refractory to subsequent injections of histamine. In only one dog did the histamine elicit a marked secretory response of watery acid gastric secretion after no response to mecholyl.

The varied responses in gastric secretion to the administration of mecholyl in this study were very similar to the extreme variations in the volume and acidity of the gastric juice obtained after the histamine or test-meals in monkeys<sup>13</sup> or in man.<sup>14, 15, 16, 17, 18</sup>

## CONCLUSIONS

1. The administration of large doses of mecholyl in aqueous solution, or embedded in beeswax produces an acid gastric secretion in most dogs.
2. The intramuscular injections of mecholyl in beeswax definitely prolonged the continuous secretion in 33 per cent of the dogs, and in approximately 70 per cent of the animals, the juice obtained was more acid and of greater volume than that obtained following the subcutaneous injection of mecholyl in aqueous solution.
3. The failure to elicit a secretory response to the same dose of mecholyl or histamine after the initial secretion had declined, suggested that the secretory apparatus had become refractory to further mecholyl or histamine injections. A possible explanation for this state was discussed.
4. The variations in response to mecholyl in dogs were similar to those observed by other workers following the injection of histamine or test-meals in monkeys and in man.

Acknowledgments are made to Merck & Company for supplying the mecholyl; and to Hoffmann-La Roche for supplying Prostigmine.

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## PROLONGED ACHLORHYDRIA FOLLOWING DIAGNOSTIC GASTROINTESTINAL ROENTGEN STUDIES\*: REPORT OF A CASE

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Transient achlorhydria of variable duration has been produced after irradiation therapy for peptic ulcer<sup>1-23</sup>. Palmer<sup>19</sup> has observed an absence of free hydrochloric acid up to 405 days. Prolonged achlorhydria, particularly that resulting from diagnostic roentgen studies, has not been previously reported. Therefore we feel that the following case study deserves presentation.

TABLE 1  
*Fractional gastric analysis*

	JUNE 16, 1943	JUNE 26, 1943	JULY 15, 1943
Degrees free HCl	0	0	0
	0	0	0
	16	16	10
	16	18	20
	0	20	14
	0	12	12
			30
	alcohol	alcohol	alcohol
Degrees total acidity	10	16	20
	8	12	23
	26	18	24
	28	28	40
	18	28	38
	22	28	52
			50

### CASE REPORT

W. C. W., a 30-year old veteran, was hospitalized June 13, 1947 because of a history of a recurrent duodenal ulcer initially diagnosed by roentgenographic and fluoroscopic examination in April 1943. Subsequent transfers with "repeated x-ray and prolonged fluoroscopic examinations" showed a normal stomach, duodenum and gall bladder. Fractional gastric analyses with an alcohol test meal were reported as shown in Table 1.

A denuded area two inches in diameter with an inflammatory border was first noted on the skin of the lower left posterior thorax in July 1943. It caused an itching and

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burning sensation. On admission the lesion was still present and showed atrophy, telangiectasis and pigmentation. Except for the presence of epigastric tenderness and repeated absence of free hydrochloric acid within the stomach (see Tables 2 and 3), the physical examination and laboratory studies were otherwise negative.

The lesion was excised and replaced by a skin graft. Microscopic appearance of the excised skin was compatible with radiation scar. With some improvement and 20 pound weight gain the patient was discharged from the hospital December 23, 1947.

TABLE 2  
*Fractional gastric analysis*

	JULY 14, 1947	JULY 21, 1947	NOV. 7, 1947	DEC. 22, 1947
Degrees free HCl	0	0	0	0
	0	0	0	0
	0	0	0	0
	0	0	0	0
	histamine	histamine	alcohol	histamine
Degrees total acidity	5	20	15	16
	9	5	8	9
	12	8	4	6
	6	9	20	6
			16	

TABLE 3  
*Nocturnal secretion studies*

	OCT. 24, 1947	NOV. 4, 1947
	cc.	cc.
Total volume.....	470	260
Degrees free HCl.....	.0	0
Degrees total acidity.....	22	30

#### DISCUSSION

The case presented impressed us as an interesting observation from two points of view:

(1) The apparent development of an achlorhydria, persistent for three and one-half years, following repeated routine gastrointestinal roentgen studies; and

(2) The confirmation of the theoretical belief that a prolonged achlorhydria can conceivably be produced by irradiation but at the expense of damage to the skin and internal organs.

It appears that frequent concerted attempts to demonstrate a peptic ulcer created a true achlorhydria which has persisted for more than forty-two

months. We realize that this phenomenon could develop spontaneously. However, in an individual who previously yielded normal quantities of free hydrochloric acid and then became unresponsive to alcohol or histamine, it is reasonable to implicate the radiation.

Bockus<sup>21</sup> states "that x-ray dosage sufficient to bring about a prolonged reduction in gastric acidity is not without the danger of permanent damage to the skin and abdominal viscera and might possibly bring about an x-ray cachexia". This theoretical postulation is confirmed by the case reported. Ivy, Snell and others<sup>22, 23, 24</sup> were not convinced that irradiation therapy for gastric hyperacidity was of value because of its destructive effect on the gastric mucosa. We were unable to evaluate the patient's clinical response by further roentgen studies because of the presence of a roentgen ray dermatitis. His symptoms likewise could not be accurately interpreted in view of the possible injury to the internal organs or radiation sickness. Furthermore, the patient had a confirmed psychosomatic background with emotional immaturity.

#### CONCLUSION

1. A case of prolonged achlorhydria following repeated routine roentgenographic studies is presented.

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## EDITORIAL

### THE VERY CAREFULLY SELECTED PATIENT

How often one reads in a paper that the poor results of a certain operation could be avoided by "a very careful selection of the patients." Perhaps the author implies that his results have not been so bad as those of other physicians because he selected his patients so wisely. How good this sounds, but how much does it mean?

After forty years of reading that patients should be selected carefully, and then searching in vain through the article to find a single word as to how the author did his selecting, the writer has got to the point where he hates to see those two words "carefully selected"; they disturb him. What disturbs him also is that the men who keep emphasizing the all-importance of selecting for, let us say, subtotal gastrectomy, those patients who will not promptly return with a jejunal ulcer, are not gathering the statistics which alone would tell us if there is any criterion for the selection of the patients. This is perhaps the most important single bit of research work that a gastroenterologist or gastric surgeon could have done for us in the last twenty years, but except for work reported by Vanzant and her associates<sup>1, 2</sup> in 1933 and 1936, we cannot remember that anyone has attempted to give a good answer to the question. Incidentally the statistics just quoted showed no correlation between the pre-operative acidity and pepsin content of the gastric juice and the incidence of recurrent ulcer.

Many readers may say, "But we do know something about selecting patients who have ulcer. Every surgeon fears operating on the very tense nervous man, or the young man, or the man with a high gastric acidity. He does not so much fear operating on the older man or the man with a penetrating or obstructing ulcer or the man with low gastric acidity." True, but where are the statistics to prove that any of these hunches are correct?

Why does not some earnest young gastroenterologist begin right now, studying carefully several hundred patients with ulcer before gastroenterostomy or subtotal resection or vagotomy, and then following up the results through the years? Such a worker should get the help of a statistician who will see if there is any correlation between the result obtained after surgery and perhaps the patient's age, body build and temperament, or posterior penetration of the ulcer, pyloric obstruction, duration and severity of ulcer symptoms, gastric acidity, amount of acid secreted in the first part of the night, or the peptic activity of the gastric juice.

Might it not be a good thing if every time a physician or surgeon finds himself

saying that patients ought to be better selected, he would stop short and ask himself, "Do I really know from long experience and rigid statistical studies what the indications are for and against this operation? Do I really know that the incidence of jejunal ulcer is less among patients who had a low gastric acidity?" It would be wonderful if we, all of us, were to do that. And it would be still more wonderful if each of us were to buy a notebook and start right now to gather such data as would eventually enable us to say how to select those patients for whom a certain procedure will almost always work well.

We physicians who, being human, tend to be full of biased opinions, hunches, prejudices, likes and dislikes and enthusiasms for pet therapies which we think, like a loved child, can do no wrong, must constantly at meetings be asking ourselves, "Did I speak then as an opinionated layman or did I speak as a true scientist from knowledge based on the absolutely honest and expert analysis of many data well gathered?" The writer knows how often under such circumstances he has had to say to himself, "What you gave was really only an impression, and now you had better keep quiet until you have enough facts of observation on which to base an opinion of some value."

W. C. A.

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## COMMENT

### THE WAYS IN WHICH EQUIVALENTS OF A DISEASE APPEAR IN A FAMILY

To the philosophically minded physician interested in unravelling the etiology of rare diseases, a helpful technic is the study of the way in which a hereditary disturbance will affect the different members of a family. Often in this way one can get a good idea of what certain equivalents are.

In the twentieth volume of St. Bartholomew's Hospital Reports, published in 1884, page 11, Samuel G. Gee reported some remarkable observations on a migrainous family. The mother, 70 years of age, had been observed for 10 years suffering from the following peculiar syndrome: From time to time she was seized with attacks of great flushing of the face and hands, great coldness of the feet, palpitation of the heart, much flatulence, and a feeling of impending death. The symptoms passed off in three or four hours, leaving the skin somewhat swollen. A few days later it would desquamate, and eventually there resulted a sort of chronic eczema of the face. These seizures occurred only in cold weather, and usually there were from two to four attacks every winter. Later, she went for five years without an attack. Aside from these spells she was well. She never had migraine, but from the ages of 30 to 61 years, she had attacks of hemianopia lasting some hours, with no vomiting but a glimmering before the eyes. There were no typical scintillating fortification figures.

The woman's son, a physician, described to Gee the peculiar troubles of his brothers and sisters. The father and his side of the family were free from any nervous disorder. The mother, whose illness has just been described, had a sister who, when young, suffered from migraine with vomiting.

The eldest son, aged 41, when about 9, would wake in the morning from a dreadful dream in which he felt "an infinity of chaos" a most frightening sense of a hopeless inability to accomplish a task, and a feeling that everything was swelling out from a center and then becoming small again. There were some visual disturbances and a headache. This trouble ceased at the age of 12. Much later in life, if he fell asleep in his chair, he woke with a sense of being overwhelmed.

The second son, aged 38, up until the age of 15, had seizures in which he had a sense of an infinite chaos, and of rolling, serpentine forms. Everything swelled and got larger and larger, and he had a sense of being overwhelmed, and of facing a hopeless struggle. Everything seemed soft and fluffy and round. He saw bright colors but never had migraine.

The eldest daughter, aged 36, from the ages of 13 to 15 had migraine with hemianopia and vomiting. Half of the objects seen were obstructed by a yellow

or green halo. She had night terrors in which she woke screaming and with a feeling of despair, as if "I had incurred a debt which I could never pay." She tended to walk in her sleep. Her hands felt swollen like boxing gloves. There was a sensation of things becoming smaller and smaller, receding, and then becoming larger again.

The third son, aged 33, had night terrors from the ages of 14 to 20; he had a feeling of a great flood sweeping across his nerves, and he heard a rushing sound. From the age of 18 on he had headache, beginning in the morning with dimness of sight, followed by glimmering hemianopia, and fortification figures. There never was any vomiting. The headaches tended to come only on a clear day following dull mild weather. He also felt overwhelmed if he fell asleep; there was a state of insensate dread or terror without known cause.

The second daughter, 30 years of age, was subject from the ages of 10 to 13 to attacks of migraine with hemianopia but no vomiting. There were feelings of things swelling and opening out, of hopeless struggle, of "woolliness" and of the hands swelling like boxing gloves. She had frightful dreams, and even at times when awake she might feel as if in a bad dream. She dreaded to go out alone. Objects looked gray to her when she was in attacks.

The fourth son, aged 27, from the ages of 15 to 17, was subject to many of the feelings already described, but he had no sick headaches.

Interestingly, the writer who for years has had typical scintillating scotomas without headache suffered throughout the early years of his life from these same dreams of horror over a task that could not be accomplished. In his case a tremendous roll of tape which he was coiling suddenly buckled and went into a snarl. Just why this should produce terror it is hard to say but it always did. The writer knows well also the nightmare of feeling that the body was swelling enormously. These dreams generally came when he had fever. His sister was distressed by the same type of nightmare. The uniformity of these dreams suggest that they depend on some pattern of the brain which is perhaps peculiar to the migrainous person.

Many of the women who complain of a certain amount of dizziness together perhaps with some feelings of detachment from the world, perhaps feelings of chilliness and wooliness of thinking and perception, are relatives of the migrainous, and some of them will be found, on close questioning, to have had migrainous headaches in their youth.

The point made by Gee is a good one and that is that if one is to get a history of migraine one may have to go back to childhood or youth. Sometimes one can get a history of cyclic vomiting in childhood or commonly, of going home from school vomiting.

It can often be of great help to a physician, when faced with a person with a bizarre syndrome, to know that he or she is migrainous and comes of a migrainous family. There is much that is remarkably uniform in the mental processes of the migrainous.

## BOOK REVIEWS

THE SURGERY OF THE COLON AND RECTUM. *Sir Hugh Devine, M.S. and John Devine, M.S.* The Williams & Wilkins Company, Baltimore, 1948, 362 pp., price \$12.50.

This is a very informative and useful book which all abdominal surgeons will want to have. It is beautifully printed and illustrated and well written. There are many plates in color. It really gives a surgeon the technical information he wants about operations on the colon and rectum.

On page 186 there is a picture of Dr. F. T. Paul who, in January 1895, described the operation that was later performed by von Mikulicz and ascribed to him.

Gastroenterologists will be particularly interested in the description of the modern operations which so commonly now save the patient's rectal sphincter. In recent years, with the help of the sulfonamides tremendous advances have taken place in the surgery of the colon, and the mortality has been greatly reduced.

This book is to be highly recommended.

CIRROSIS DE HIGADO ESTADIOS PREVIOS. *Histofisiologia Normally Patologica de Higado Pruebas Functionales y Tratamiento.* By Luis Bernardo Rabinovich. Cayetano Vergara, Buenos Aires, 1948, pp. 707.

In this large book, Dr. Rabinovich reports a personal study of a large number of patients and also summarizes much of the information which he has obtained from the literature. A large part of the book is taken up with case reports, with microphotographs of sections of the liver. Most of the tissue was taken during operations. There is a tremendous amount of information in this book, and one must congratulate the author on what he has done. One only wishes that on many pages he had given his own clinical impressions and not just the impressions which he gained from the literature.

PAIN. By Harold G. Wolff, M.D. and Stewart Wolf, M.D. Charles C. Thomas, Springfield, Illinois, 1948, pp. 86, price \$2.00

This is a splendid little book, written by two men who have done a tremendous amount of research work on the problems of pain. As one would expect, they have written a booklet which should be in the hands of every practising physician. It will help him to understand perhaps the commonest symptom of all. It is well illustrated, well written, and well documented. There is much on the new method of measurement of threshold of pain perception and on the way in which this threshold is raised by drugs. There is much new information on the segmental distribution of pain. Probably few clinicians realize how much they can tell about a diagnosis if they will only take a good history and only know what certain distributions of pain mean in the way of localizing a lesion.

FEVER AND THE REGULATION OF BODY TEMPERATURE. By Eugene F. Du Bois, M.D. Charles C. Thomas, Springfield, Illinois, 1948, pp. 68, price \$2.00.

So often when he sees a small book, the reviewer picks it up gingerly; fearing that because of limitations of size and poor judgment in picking the subjects for inclusion, the book will be of little, if any, value to either specialists or general practitioners or internists. Accordingly, it is with great joy that one picks up the little monographs of the American Lecture Series edited by Robert F. Pitts of Syracuse and published by Charles Thomas. All those that we have seen so far have been excellent and of value even to the specialist. For instance, in this book on Fever every practising physician should look at Figure 1 taken from Ivy's work with his students. It shows the oral temperatures of 276 medical students seated in a class between 8 A.M. and 9 A.M. The mean temperature was 98.1° F. but the commonest temperature was about 98.3° F. The range was from 96.6° F. to 99.4° F., and that is the most important point which thousands of physicians forget today. Often it does not occur to them that the nervously upset woman with a temperature of 99.6° F. may be perfectly normal.

Dr. Du Bois, of course, knows well whereof he speaks, and every page of his book is delightful.

**MEDICAL HYPNOSIS.** Volume I. The Principles of Hypnotherapy. Volume II. The Practice of Hypnotherapy. *Lewis R. Wolberg, M.D.* Grune & Stratton, Inc. New York, 1948, pp. 449 (vol. I), price \$5.50, pp. 513 (vol. II), price \$6.50.

This is a welcome book, now that quite a few psychiatrists are testing the value of hypnosis in their practice. As Wolberg says, some men are enthusiastic about it and others condemn it severely.

In volume I the author takes up in detail the methods of inducing hypnosis and he gives transcriptions of what happened during hypnotic sessions.

Volume II contains three complete transcribed case histories which will enable the reader to follow the various stages of treatment as carried out by Dr. Wolberg. Wolberg feels that hypnosis speeds up the practice of psychotherapy but it cannot be regarded as a "cure-all." A number of emotional problems fail to respond to hypnotherapy and require a longer analytic approach. Interestingly, Wolberg points out that psychotherapy is difficult if the physician himself is a bit psychopathic or neurotic or difficult to get along with.

These volumes are interestingly written and there is much in them to hold the interest of any physician. There is much also on the psychoneuroses and on the handling of neurotic patients without the help of hypnosis.

As every good psychiatrist knows, one can often work a miracle of healing in a few minutes with hypnosis, let us say in the case of a patient with a hysterical contracture, but this doesn't mean that the patient is cured. From then on the physician must try to help the patient with the situation that brought on the hysterical paralysis or seizure.

On page 369 in volume I there is an interesting statement to the effect that one can sometimes help schizophrenics if one can establish some friendly contact with them. Most of these people are desperately fearful of any close relationship with anyone, and yet beneath the surface they may yearn for friendly and loving relationships.

Nevertheless, they ward off all contacts. Perhaps to some extent they are fearful of rebuffs.. Wolberg feels that if the physician is not too antagonistic at first to the schizophrenic's ideas, he may be able to help him a good deal.

On page 227, Dr. Wolberg suggests that when there is considerable resistance to hypnosis a light barbiturate narcosis may remove the block and help.

On page 329, Dr. Wolberg speaks of the great difficulty of doing anything for the "essential alcoholic," as he calls him. His character is too immature.

Here and there in the book the non-Freudian will be shocked at finding certain statements which will seem very odd to him. For instance, on page 223 one reads of the adolescent girl who said she was unable to chew her food or swallow it. This was supposed to be a defense against the impulse to bite off and swallow her father's penis! Premature ejaculation is thought by Wolberg to be a hysterical symptom, often a regressive form of pleasure functioning embracing both masturbation and urinary activities. "In the psyche of the individual, it often represents a form of sexual gratification equivalent to the mother's holding of the child's penis as he urinates!"

**EVERYDAY MIRACLE.** Through Intimate and Sympathetic Observation of Animals a Brilliant Scientist Illuminates the Miracle of all Life. *Gustav Eckstein*. Harper & Brothers, New York, 1948, pp. 235, price \$2.75.

As has been noted repeatedly in this column, every physician should have a little shelf beside his bed for a bit of reading every night before he turns out the light. As Osler always said, this reading should be perhaps on the borderlines of medicine. It should be designed to strengthen and reinforce and bring out that tendency to a philosophical thoughtfulness and insight which is found in every fine physician, especially as he grows older.

Eckstein, a physiologist, has for years been writing delightful stories, many of them about animals, for whom he has the greatest sympathy and understanding. They in turn come to love him. In his laboratory he always keeps some fifty canaries that fly around freely. He has known these canaries intimately from birth to old age, and he writes delightfully about them and other birds and animals whom he has come to know well.

Perhaps most delightful in this series of stories is the tale of the macaw who was remarkably human. No physician should ever miss anything that has been written by Gustav Eckstein.

**GLOMERULAR NEPHRITIS:** Diagnosis and Treatment. *Thomas Addis, M.D.* The Macmillan Company, New York, 1948, 338 pages, price \$8.00.

Sometimes the reviewer is delighted with the contents of a book, sometimes with the charm of its English, and sometimes in addition he delights in seeing how the author carried out his research and how he organized his work. This book delights for all three reasons. Back in 1911, Thomas Addis came from Edinburgh and Berlin and Heidelberg to join the faculty of Stanford University. For over 25 years he has concentrated his attention on problems of the diagnosis and handling of diseases of

the kidneys. All through these years he has studied the function of the kidneys in health and disease, both in animals and in man. Years ago one day, when confronted with a boy all bloated with edema, Addis measured the amount of protein being put out in the urine and found it was much more than what the physician was allowing the patient in his diet. Little wonder that the patient's serum proteins were too low, and that he was edematous. Then and there Addis began to argue for a saner treatment of many patients with nephritis.

As Addis says, during the years, because of the inability of clinic patients to pay for large amounts of blood chemistry, he has been forced to devise a series of simple tests which any physician can carry out quickly. He has not tried to cover the literature on glomerular nephritis, but he has written this book about the researches which he and his students through the years, have carried out.

In order to study the value of the various tests for renal function, Addis and his students have studied these tests on rats from which varying amounts of kidney tissue have been removed surgically. For instance, if one kidney is removed, theoretically any good test for kidney function should show a result half of what it was before. Actually, on page 116 Addis concludes that the best method is the determination of the concentration of creatinine in the serum. Creatinine clearances seem to vary closely with the best estimates of the quantity of effectively functioning renal tissue.

The average physician has been trained to assume that if there is albumin in the urine there must be serious injury to the kidney. Addis has worked for twenty-five years to find out if in an individual case the injury to the kidney is serious or inconsequential.

On page 189 Addis says that there are three cardinal signs indicating glomerular nephritis: one, is the gross appearance of the urine, the other is edema, and the third is hypertension. The patients say the urine looks like coffee. It is an acid solution of acid hematin. Furthermore, it is opaque and this opaqueness or cloudiness is due to hundreds of millions or billions of red blood cells, tubule cells and casts.

This book is filled with information, backing up Addis' many statements as to the nature of nephritis, what it does to the body chemistry, and what it means to prognosis and diagnosis, and to treatment. This is a grand book for any man to study who wants to go on into that field of research where the laboratory and the clinic meet. Addis is to be complimented on a magnificent job well done.

# ABSTRACTS OF CURRENT LITERATURE

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### Diseases of the digestive system. Med. Clinics N. Am. (Mar.) 1948.

This entire issue is devoted to a symposium on gastrointestinal disease. We regret that because of limitations of space, we are unable to publish individual abstracts of these papers. The authors and titles of the articles included are as follows:

D. L. Wilbur, G. Cheney and C. Mathewson—Clinical Conference on Vagotomy  
A. L. Bloomfield—Peptic Ulcer  
E. Wayburn—The Medical Management of Massive Upper Gastrointestinal Hemorrhage  
C. D. Armstrong and D. L. Wilbur—Malignant Disease of the Stomach Simulating Gastric Diverticulum  
G. Cheney—The Diagnosis and Treatment of the Common Forms of Stomatitis  
G. W. Nagel—Lesions of the Esophagus  
G. Crile, Jr.—Medical Aspects of Intestinal Obstruction  
R. L. Haden and D. Bortz—Anemia in Diseases of the Intestinal Tract  
T. E. Jones—Differential Diagnosis of Intra-abdominal Pain

E. N. Collins—The Diagnosis and Treatment of Irritable Colon  
E. N. Collins and F. L. Bynum—Amebiasis and Indeterminate Ulcerative Colitis  
H. R. Rossmiller and H. M. Messenger—Regional Enteritis: Diagnosis and Treatment  
C. R. Hughes and E. J. O'Malley—Roentgenologic Diagnosis of Tumors of the Large Intestine  
J. C. Root—Roentgenologic Diagnosis of Tumors of the Small Intestine  
J. C. Sinclair and R. F. Farquharson—Jaundice  
J. A. Dauphinee and W. R. Campbell—Serum Proteins in Hepatic Disease  
R. C. Dickson—Acute Infections of the Liver  
E. J. Maltby and T. Owen—Diseases of the Biliary Tract  
J. A. Dauphinee and J. C. Sinclair—Chronic Hepatitis. The Cirrhoses  
K. J. R. Wightman—Diseases of the Pancreas  
H. C. Hopps and W. C. McClure—Clinicopathologic Conference

EDITOR.

## STOMACH

PALMER, E. D. Observations on the treatment of chronic hypertrophic gastritis with shortwave diathermy. *Rev. Gastroenterol.*, 15: 233 (Mar.) 1948.

As a result of study of 30 hospitalized patients with chronic hypertrophic gastritis, it is concluded that shortwave diathermy as applied had no significant therapeutic effect on the clinical or gastroscopic course of the disease. No immediate effect on the secretory activity of the stomach in these patients was noted. Histologic study of the stomach in one patient likewise showed nothing to suggest effect from the shortwave application.

C. WILMER WIRTS, JR.

GRAHAM, R. M., ULFELDER, H. AND GREEN, T. H., JR. The cytologic method as an aid in the diagnosis of gastric carcinoma. *Surg. Gyn. Obs.*, 86: 257 (Mar.) 1948.

This paper is a preliminary report of the authors' experience with a diagnostic measure which may be of value in discovering early gastric carcinoma—cytologic examination of gastric fluid for the presence of malignant cells. In the series of 50 cases reported, 24 had carcinoma of the stomach, and smears were positive in 15 of these. Five out of 7 patients with resectable lesions of the stomach had positive smears. In the 26 other cases, no evidence of cancer was shown.

FRANCIS D. MURPHY.

GOLDEN, R. AND STOUT, A. P. Superficial spreading carcinoma of the stomach. *Am. J. Roent. Rad. Therapy*, 59: 157 (Feb.) 1948.

Since carcinoma of the stomach is an epithelial growth arising in the mucous membrane except in rare instances, it may grow in some cases without changing the gastric contour or movements. Malignant tumors have two basic growth characteristics: (1) mass producing and (2) infiltrating. The superficial type, spreading into the mucosa and submucosa, was found in 14 per cent of 200 cases of carcinoma. Of these, 80 per cent were ulcerating and 20 per cent non-

ulcerating. In the limitis variety, spread occurred in 2.5 per cent of 200 cases.

The superficial spreading carcinoma arises in and grows along the mucosa replacing the normal mucous membrane obliterating the normal mucosal folds and smoothing out the surface. It may be limited to the mucous membrane alone, but usually it penetrates through the muscularis mucosa. The authors found 31 cases of superficial spreading carcinoma of the stomach in a period of 10 years. One stomach contained two superficial spreading cancers. In 2 cases, mixed types of carcinoma were present. In 30 of the 31 cases it involved the lower half of the stomach. In 12 cases the cancer developed around an open peptic ulcer; in 2 instances the cancer developed in the mucous membrane over the scar of a healed peptic ulcer. In only 4 of the 31 cases the superficial spreading cancer was present without an active ulcer. In 9 of 11 cases gastroscoped, evidence suggestive of cancer was found. Of the 29 cases roentgenographed, 24 revealed carcinoma on pathologic examination; of these, 20 were recognized by the roentgen examination. A 6-hour gastric residue was present in 21 of 26 cases.

It is emphasized from this study of 31 cases that difficulty was not encountered in detection of an abnormality on roentgen examination but rather in ascertaining whether cancer was or was not present in an obviously abnormal stomach.

MAURICE FELDMAN.

SANDBERG, I. R. Postoperative emptying difficulties in direct connection with astic resection. *Acta Chir. Scand.*, 95: 286 (Mar.) 1947.

Five cases of gastric resection for ulcer are reported, in whom there was a delayed gastric motility postoperatively. The immediate postoperative delay is due to edema of the stroma or slit in the mesocolon. This is of a transitory nature and is best treated by gastric aspiration. Any disturbance in the blood chemistry must be recognized immediately and corrected at once. Secondary laparotomy is usually unnecessary and ineffectual.

PHILIP LEVITSKY.

WAHREN, H. Total resection of the carcinomatous stomach. *Acta Chir. Scand.*, 95: 193 (Mar.) 1947.

The technique of total gastrectomy is described. In a series of 9 cases thus treated, 4 died from metastases within 1 year. The operative mortality is no greater than for partial resection. It is doubtful whether the curability of cancer of the stomach will be increased by the more radical operation because of the difficulty of early diagnosis.

PHILIP LEVITSKY.

COMFORT, M. W., KELSEY, M. P., AND BERKSON, J. Gastric acidity before and after the development of carcinoma of the stomach. *Proc. Staff Meet. Mayo Clinic*, 23: 135 (Mar.) 1948.

The data were obtained from the records of 277 patients who have had one or more gastric analyses at least 2 years previous to the diagnosis of cancer. The interval between the initial analysis of gastric contents and the diagnosis of gastric carcinoma averaged 11.2 years. The cases included 203 men and 74 women. Most of these patients had had gastrointestinal complaints at the time of original examination. Twenty-three cases had been diagnosed as pernicious anemia, 30 as duodenal ulcer, and 33 as gastric ulcer. It appears that the incidence of ulcer and pernicious anemia is higher in this series than in other published series of gastric cancers. Of these 277 patients only 150 (54.2%) had free hydrochloric acid, whereas 127 (45.8%) had achlorhydric gastric contents. Before cancer developed, the incidence of anacidity was greater by 23 per cent and the mean free acidity was smaller by 3 clinical units than would be expected for a group of normal patients of the same age and sex. At the time of the diagnosis of cancer the percentage of patients with achlorhydria had increased from the initial 45.8 per cent to 68.8 per cent. Present evidence supports the hypothesis that atrophy of the gastric mucosa is responsible for the depression of secretory activity before the development of gastric cancer. Gastric carcinomas in this series of cases developed in patients with lower than normal gastric secretory activity and many of them in un-

healthy stomachs, diseased with chronic gastritis and peptic ulcer.

FRANK NEUWELT.

TATE, R. W. AND FUSARO, W. J. Neurofibroma of the stomach. *Am. J. Surg.*, 75: 607 (Apr.) 1948.

Gastric neurofibromata are extremely rare benign tumors which arise from the nerve structures in the wall of the stomach. They occur more frequently on the lesser curvature near the pylorus, and generally grow outward from the coats producing a bulging mass into the peritoneal cavity. They may project inward and eventually ulcerate as a result of the overlying tension. They grow slowly, never infiltrate, "shell out" easily, frequently degenerate, and in 10 per cent of cases become malignant. Macroscopically, they are pearly-grey in color, rather hard, and on section the surface appears homogeneous, moist and glistening. Microscopically, they appear to arise from the Auerbach and Meissner plexuses, and exhibit proliferation of nerve filaments arranged in thick bundles or tracts.

Neurofibroma of the stomach does not present any characteristic symptom-complex that might establish a diagnosis. Symptoms may resemble those observed in ulcer even to hemorrhage, while lesions near the pylorus may present obstructive features, and intussusception where the tumor is pedunculated. A correct preoperative diagnosis is difficult but it may be suggested when associated with cutaneous neurofibromatosis and the hereditary tendency. Differentiation between a benign and malignant gastric tumor requires the application of several criteria of which roentgenoscopy and gastroscopy are particularly valuable. The treatment of choice is surgery after proper preoperative preparation. Bearing in mind the multiplicity of neurofibromatosis, a careful search for other intra-abdominal conditions should be carried out at the time of operation. A case of solitary neurofibroma of the stomach is reported.

MICHAEL W. SHUTKIN.

MAUR, M. The value of gastroscopy in the study of postoperative gastric symptoms. *Arch. argent. de enferm. d. ap. digest.*

y de la nutricion, 22: 311 (Sept.-Oct.) 1947.

Of the 157 patients who were studied, 101 had a gastro-enterostomy and the remaining 56 had a partial gastrectomy. The patients came to examination 20 days to 33 years after the operation. No pathology was discovered in the stomach, duodenum or jejunum of 50 patients. Diagnosis was made by gastroscopy in all cases of gastritis (47 cases), inflammation of the stoma (36 cases), gastric ulcer (8 cases) and carcinoma of the stomach (1 case). In addition, correct gastroscopic diagnoses were made in 9 out of 11 cases of marginal ulcers, 2 out of 15 cases of jejunal ulcer, 2 out of 13 cases with polypi, and 2 out of 3 instances of fistula.

#### ALOYSIO FARIA.

#### BOWEL

COLE, W. H. Intestinal obstruction. Can. Med. Assoc. J., 58: 241 (Mar.) 1948.

The pathology, abnormal physiology, diagnosis and treatment of intestinal obstruction are reviewed. When the diagnosis of obstruction is made, decompression of the bowel and the intravenous administration of fluids should be started immediately. If the patient has eaten, the stomach should be evacuated with a large stomach tube to remove all food particles. If the diagnosis of obstruction by adhesions is established, decompression may be continued for many hours in the hope that the point of obstruction will be released. The patient should be watched carefully for signs of strangulation; an increase or the persistence of pain and the development of tachycardia usually justify discontinuance of conservative treatment and the adoption of operative therapy.

In certain types of lesions, for example intussusception and volvulus, operative treatment is indicated as soon as the patient's condition will tolerate it. Another strong indication is the presence of a complete obstruction in the colon, regardless of the type; the procedure of choice initially is colostomy. During operation it is usually necessary to give large quantities of blood to replace the considerable loss of blood or plasma through the wall and lumen of the intestine. Gastro-intestinal decompression

must be maintained after operation, usually for 72 hours.

Improvement in mortality rate in intestinal obstruction is dependent upon (a) intelligent use of gastro-intestinal decompression; (b) early diagnosis; and (c) careful attention to imbalances related to fluid, electrolytes and blood protein. Operative technique and the relative incidence of strangulation are important accessory factors.

JOSEPH B. KIRSNER.

LYONS, A. S. The sigmoid as a source of right-sided symptoms. Ann. Surg., 127: 398 (Mar.) 1948.

Eighteen cases are reported wherein lesions in the sigmoid and recto-sigmoid caused symptoms and signs on the right side of the abdomen. Usually the diagnosis was that of acute appendicitis; most often the pathological lesion was diverticulitis or carcinoma leading to peritonitis or abscess formation. The cases illustrate the following probable mechanisms for the location of symptoms: 1) sigmoid lying over on the right of the midline, 2) perforation of the right wall of the recto-sigmoid with spillage of fluid towards the right, 3) peri-sigmoidal abscess extending to the right, 4) adherence of right-sided structures to the sigmoidal lesion, 5) situs inversus.

LEMUEL C. McGEE.

MCGUFF, P., DOCKERTY, M. B., WAUGH, J. M., AND RANDALL, L. M. Endometriosis as a cause of intestinal obstruction. Surg. Gyn. Obs., 86: 273 (Mar.) 1948.

Sixteen cases of intestinal obstruction caused by endometriosis are presented as well as a pathologic study of these cases. This condition should be suspected in women between the ages of 30 and 50 showing intestinal obstruction with no weight loss but with acquired dysmenorrhea, menstrual periodicity of symptoms, sterility, and rectal or pelvic pain. Severe constipation, lower abdominal pain, and distention are almost always present. Endometriosis associated with intestinal obstruction is usually confirmed if a firm tumor is found in the rectovaginal septum or if tender palpable nodules are present and the uterine fibroids and bilat-

teral ovarian cysts are palpable. Treatment is surgical, consisting usually of bilateral oophorectomy or of panhysterectomy with or without colostomy.

FRANCIS D. MURPHY.

GILCHRIST, R. K. AND DAVID, V. C. Prognosis in carcinoma of the bowel. *Surg. Gyn. Obs.*, 86: 359 (Mar.) 1948.

Of 200 patients operated on more than 5 years ago for carcinoma of the large bowel, 114 (57%) were known to be alive 5-10 years later. When lymph node involvement is present, the widest possible resection of the mesentery is necessary, rather than the usual V-shaped wedge. The authors deem it unwise to consider anything less than a 5-year survival as a cure because of the appreciable percentage who develop recurrences in the fourth and fifth year.

FRANCIS D. MURPHY

MCCULLOUGH, J. Y. Survey of some aspects of appendicitis. *Am. J. Surg.*, 75: 453 (Mar.) 1948.

The effects of penicillin were analyzed in a series of 616 appendectomies operated upon over a 4-year period. The cases were classified as follows: acute 278; perforated 105; abscessed 13; subacute 168; catarrhal 4; mechanical 4; and recurrent 44. The mortality rate for the entire group was 1.7 per cent. There was a 48 per cent decrease in the mortality of all types after the use of penicillin. In those patients with frank abscess and perforation, the decrease in mortality after penicillin was 70.9 per cent.

The Miller-Abbott tube for small intestinal intubation has proven of great value in instances of paralytic and mechanical ileus. The principle causes of death were peritonitis and pulmonary embolism, the latter arising from a site of phlebothrombosis.

The clinical effects of penicillin in mixed infections is striking, and with larger doses to overcome the penicillin-neutralizing function of the *Escherichia coli* greater efficacy may be expected.

MICHAEL W. SHUTKIN.

with particular reference to cancer and ulcerative colitis. *Am. J. Surg.*, 75: 384 (Feb.) 1948.

In rectal and rectosigmoid carcinoma, surgical experience with abdominal resection with removal of the tumor and lymphatics and reestablishment of intestinal continuity is as yet immature and probably less efficient than the standard abdomino-perineal resection. In cancer of the left colon with numerous and enlarged lymph nodes, a considerably larger segment of colon is removed by extending the abdomino-perineal operation, thus enlarging the opportunity of getting wide of the lesion. Where possible, after segmental resection, the transverse colon is joined to the terminal pelvic colon. In malignancies of the right colon the sentinel node at the inferior border of the pancreas along the mesenteric vessels should be sought out and removed.

The present study reflects the experience with low anastomosis and preservation of sphincteric function in carcinoma of the rectum and rectosigmoid, benign tumors, diverticulitis and ulcerative colitis. The majority of such cases were operated upon employing the end-to-end suture technique. Healing in the direct suture anastomosis is rapid, and patients leave the hospital in one week. The technical surgical details for this operation has been described elsewhere. Excision of the terminal pelvic colon and upper rectum and restitution of intestinal continuity has been accomplished in a one-stage operative procedure with a satisfactory mortality. Functional sphincteric control is complete after the suture operation, but sometimes fails following the pull-through procedure. Sphincter-saving operations are contraindicated in low-lying lesions because of local recurrence, but are suitable for lesions above 8 cm. Local recurrence was observed in 7 of 51 operated patients. The experience in 13 cases of ulcerative colitis, with primary restoration of intestinal continuity after excision of subtotal lengths of the colon and rectum, was gratifying.

MICHAEL W. SHUTKIN.

CANTOR, M. O., PHELPS, E. R., AND ESLING, R. H. Effect of intestinal gases upon

WANGENSTEEN, O. H. AND TOON, R. W. Primary resection of the colon and rectum

balloons of intestinal decompression tubes. Am. J. Surg., 75: 441 (Mar.) 1948.

Rubber membranes are permeable to gases and the rate varies with the type of rubber and gases used. Gases in rubber behave similarly to gases in organic liquids, and the gas goes into solution in the rubber on the one side of the membrane and then emerges on the other side by evaporation. The law of diffusion of gases applies to the passage of the gases through the rubber membrane, and the results of extensive researches were formulated into Henry's law and Fick's law.

The authors have studied the balloons of intestinal decompression tubes by using carbon dioxide because this gas and hydrogen sulfide are apt to be troublesome during intubation because of permeability and pressure equalization within the balloon. This increased amount of gas within the balloon of the long intestinal decompression tube results in a bulging of the bowel wall around it, sometimes causing a complete obstruction and even a tear in the anastomosis or bowel wall. These hazards have been eliminated by the construction of the Cantor tube. An absolute prevention to the accumulation of the gas which permeates through the wall of the balloons of intestinal tubes consists merely in applying the tie to the balloon in such a fashion that the mercury remains trapped but air can enter and leave. Furthermore, all balloons should be made of neoprene-G rubber because it is less permeable to carbon dioxide than latex rubber. With the Cantor tube, less than 0.2 per cent of the cases intubated demonstrated gas within the balloons.

MICHAEL W. SHUTKIN.

D'ANTONI, J. S. Chronic diarrheas. Am. J. Surg., 75: 332 (Feb.) 1948.

Chronic diarrhea is perhaps the most grossly mismanaged condition in all of medicine. Diarrhea and dysentery are characterized by unformed stools which may contain mucus, pus and blood. However, the dysenteric stool also contains cellular debris, small quantities of feces, or none at all, and the discharge is always associated with tenesmus. On the other hand, the diarrheic

stool whether acute or chronic is chiefly fecal in composition.

Amebiasis is the most common cause of chronic diarrhea even though constipation is an important part of the clinical picture. The second most frequent cause of chronic diarrhea is shigellosis, although no more than 20-30 per cent have a history of previous dysentery. Brucellosis in its intestinal form is becoming known as an important cause of chronic diarrhea. The coexistence of two or three different types of intestinal infection occurs not uncommonly. Common to the symptomatology of amebiasis, shigellosis, and brucellosis are nervous irritability, fatigue, low grade fever, vague abdominal symptoms, arthritic manifestations, and muscular pains. In amebiasis, the parasite has a special predilection for the cecum and rectosigmoid area, and the character of the symptomatology depends upon the location of the infectious process. Amebiasis does occur in children and has bizarre and distinctive symptoms.

The etiologic investigation of chronic diarrhea depends mainly on laboratory procedures and should include (1) study of the spontaneous stool, (2) Frei test, (3) blood studies, (4) sigmoidoscopy, (5) stool examination after purgation, and (6) special tests for brucellosis.

Initial therapy for chronic diarrhea in amebiasis includes administration of a high potency multiple vitamin preparation and emetine, carbarone, diodoquin, chiniofon, vioform, penicillin, or sulfonamides. Shigellosis and brucellosis are treated with vaccines, administered subcutaneously in successively larger, but cautiously increased, doses at intervals of five to seven days, in conjunction with the Jones sugar-free diet.

MICHAEL W. SHUTKIN.

WHITMORE, W. H. Duodenal diverticula with ulceration. Am. J. Roent. Rad. Therapy, 59: 343 (Mar.) 1948.

The author found 18 cases of duodenal diverticula in 5,712 gastrointestinal roentgen examinations among Naval personnel. In 645 gastrointestinal examinations in civilian practice, 25 cases were observed. Of the original 18 cases 16 had no symptoms and

2 had hemorrhages. Of the 25 cases observed in civil life 5 had symptoms, one of which had a history of bleeding. The author points out that ulceration may occur in a diverticulum which may or may not contain atypical gastric mucosa, however most diverticula cause no symptoms. Two cases of ulceration in a duodenal diverticulum with hemorrhage are reported.

MAURICE FELDMAN.

RODGER, D. E. The challenge of colitis.

*Can. Med. Assoc. J.*, 58: 153 (Feb.) 1948. Six cases with ulcerative colitis are described, illustrating the lack of knowledge concerning the etiology and treatment of the disease. The value and limitations of medical and surgical treatment are considered briefly. The author believes that further study of the reflex pathways leading to vasoconstriction of the colon is the most promising approach to the solution of the problem.

JOSEPH B. KIRSNER.

HULTBORN, K. A. Treatment of cancer of the colon. *Acta Chir. Scand.*, 95: 215 (Mar.) 1947.

In the 6-year period ending in 1946, 142 patients were treated for carcinoma of the colon. Ninety-three radical operations were performed. In 63 left-sided cases the mortality was 8.6 per cent. In 30 cases of right-sided tumors, the mortality was 23.3 per cent. The operation consisted of a wide resection with end-to-end anastomosis. All cases of acute ileus were first subjected to a cecostomy. In other cases, when the intestine was not empty at time of operation or if a constriction at the anastomosis was anticipated, a cecostomy was also performed. Direct anastomosis has the advantage over the Block-Mikulicz operation in that the operation can be more radical, and can be done in one-stage.

PHILIP LEVITSKY.

HIERTONN, T. Septic appendical peritonitis and fluid balance. *Acta Chir. Scand.*, 96: 224 (Dec.) 1947.

The mortality rate of perforated appendicitis with peritonitis has dropped from 33 per cent prior to 1940 to 16 per cent since that

date. This is due to the mode of treatment adopted which includes the following procedures: 1) immediate treatment for shock; 2) early operation without drainage; 3) restoration of fluid balance with intravenous glucose, blood, plasma and chlorides; 4) chemotherapy, using sulfonamides and penicillin; 5) Wangensteen suction in distention; and 6) early post-operative movement and exercise.

PHILIP LEVITSKY.

#### LIVER AND GALL BLADDER

LLOYD, C. W. AND WILLIAMS, R. H. Endocrine changes associated with Laennec's cirrhosis of the liver. *Am. J. Med.*, 4: 315 (Mar.) 1948.

A study has been made of endocrine functions in 71 patients with cirrhosis of the liver. These patients were graded I, II, and III according to the severity of their liver disease. Of the subjects, 55 were males and 16 were females. Clinical endocrine changes observed in the male subjects consisted of decreased libido and potency, atrophy of the testicles, decreased body hair and gynecomastia. Telangiectasia and "liver palms" were also regarded as possibly being related to altered endocrine function. There was a decrease in libido and potentia in 37 male subjects and a decrease in axillary hair in 46 of the 55 male patients. Testicular atrophy was present in 36 (65%) of 55 patients while 75 per cent of the severe cases of cirrhosis had atrophy of the testicles. Gynecomastia was present in 23 of 55 patients. Following the injection of testosterone propionate intramuscularly, 4 male subjects had no increase in the quantity of 17-ketosteroid substances in the urine, 12 had significant increase in the total excretions of androgens.

In the female there were alterations in menstrual pattern, sexual drive, body hair, the uterus and in other target organs of estrogen including the breasts. Seven of eight female subjects who were in the reproductive age had menstrual abnormalities. Four of these patients had amenorrhea of infrequent bleeding.

The data accumulated suggests that the liver may participate in steroid metabolism

in the following manner: (1) in the interconversion of estradiol and estrone and their conversion to estriol, (2) in the formation of inactive oxidative products from estrogen, and (3) in the conjugation of estrogens for inactivation and excretion. With a marked decrease in these functions of the liver free estrogen will accumulate in the blood and urine. Associated with this there occurs a diminution in the release of follicle stimulating hormone, a suppression of spermatogenesis and follicle maturation, and estrogenic stimulation of target organs. The decrease in the inactive oxidative products of estrogen leads to a decreased release of luteinizing hormone and possibly adrenotrophin from the pituitary. This, in turn, will result in menstrual abnormalities, decreased activity of the cells of Leydig, and decreased adrenal function with loss of axillary hair and diminished urinary 17-ketosteroid excretion.

MICHAEL W. SHUTKIN.

SILER, V. E. AND ZINNINGER, M. M. Surgical treatment of carcinoma of the ampulla of Vater and the extrahepatic bile ducts. *Arch. Surg.*, 56: 199 (Feb.) 1948. Eight proved cases of ampullary carcinoma are reported with a resectability rate of 50 per cent and a 10 year mortality rate of 87.5 per cent. In addition, 10 proved cases of carcinoma of the extrahepatic bile ducts are reported with a resectability rate of only 10 per cent and a 10 year mortality of 100 per cent.

Early diagnosis is imperative if treatment is to be improved. The rarity of these diseases makes clinical diagnosis difficult. The significant findings in ampullary carcinoma are: (1) history of persistent epigastric discomfort or pain, (2) history of anorexia and loss of weight, (3) clinical substantiation of obstructive jaundice, (4) anemia, (5) persistent occult blood in stool, (6) presence of blood in duodenal secretion, and (7) roentgenologic "filling defect" or "reversed 3 sign" at the periampullary region.

The onset of carcinoma of the extrahepatic bile ducts is frequently acute and the principle symptoms are pain, jaundice, loss of weight, weakness, fever, chills, vomiting and occasionally steatorrhea. Early explor-

ation is necessary for confirmation of diagnosis in both types of lesions and jaundice need not be a contraindication today if the patient is properly handled. Partial cholecdochoduodenopancreactectomy is the most desirable operation.

C. WILMER WIRTS, JR.

HULTBORN, K. A. On spontaneous complete discharge of stones from the gallbladder and common duct. *Acta Chir. Scand.*, 95: 260 (Mar.) 1947.

Three cases are presented where a roentgenologic and clinical diagnosis of cholelithiasis was made. The stones were very small and consisted entirely of cholesterol. All were treated with bile salts and olive oil. One case was laparotomized about 2 months later and no stones were found. The other other two cases showed absence of stones on subsequent cholecystogram.

PHILIP LEVITSKY.

MULHOLLAND, H. B. AND EDWARDS, T. S. Recent advances, etiology and therapy of cirrhosis of the liver. *Southern Med. J.*, 41: 269 (Mar.) 1948.

The authors present a resume of the modern conception of cirrhosis of the liver as a deficiency disease, reviewing the experimental work of the last decade. An analysis of the authors' series of 26 cases is presented and a method of treatment is outlined. Diet is the *sine qua non* of therapy, but adjuncts such as intravenous or intramuscular crude liver may be important. The use of low salt diets, and the employment of ammonium chloride and mercupurine may prolong the interval between paracenteses, and result in disappearance of edema. Emphasis is placed on the importance of long continued therapy, for even under the most favorable circumstances no improvement can be expected for a considerable period of time.

ANTHONY M. KASICH.

JUDD, E. S., JR. Surgical treatment of acute cholecystitis. *Proc. Staff Meet. Mayo Clinic*, 23: 142 (Mar.) 1948. The recent trend in the treatment of acute cholecystitis, with or without stones, is early surgical intervention. Heuer was one of the

first advocates of surgical treatment of acute cholecystitis; he stressed early cholecystectomy in properly selected cases. Unquestionably, cholecystectomy is indicated in patients who have had cholecystitis and in whom X-ray examinations have revealed gall stones. However, the routine removal of gall bladders containing gall stones is not indicated, since in about 50 per cent of such cases the gall stones do not produce the symptoms. The author strongly favors early surgical intervention in proven cases of acute cholecystitis, following adequate preoperative preparation of the patient. The decision as to what operation can be accomplished is made only after the peritoneum has been incised and the situation properly evaluated. Cholecystectomy is performed whenever feasible; otherwise, cholecystostomy or partial cholecystectomy may be performed. One great advantage of this latter type of operation is that it usually permits removal of all the stones from the area of the cystic duct. The author emphasizes that a valid reason for early surgical intervention is that rupture of the gall bladder and gangrenous cholecystitis may be more common than is suspected.

FRANK NEUWELT.

#### PANCREAS

MACGUIRE, C. J. AND CONTE, A. J. Acute pancreatitis. *Ann. Surg.*, 127: 557 (Mar.) 1948.

The authors give a summary of the clinical findings in 30 patients with acute pancreatitis seen over a ten-year period. The diagnosis was supported in each instance by markedly elevated blood amylase or findings at operation or autopsy.

The peak of blood amylase levels was usually reached 12 to 24 hours after the onset of illness and varied from 207 to 3440 units. When the correct diagnosis was not recognized prior to exploratory laparotomy, the patients usually were assumed to have acute cholecystitis, perforated ulcer or acute appendicitis. Twenty-three of the patients received an operation of whom 6 died. Seven received supportive treatment, of whom 4 died. The authors believe that the edematous type of pancreatitis (no criteria given for recognition) should not be oper-

ated upon, and that the necrotic type should be operated upon after the initial shock subsides.

LEMUEL C. MCGEE.

DOUBILET, H. AND MULHOLLAND, J. H.

The surgical treatment of recurrent acute pancreatitis by endocholedochal sphincterotomy. *Surg. Gyn. Obs.*, 86: 295 (Mar.) 1948.

The purpose of this paper is to present a method for the surgical treatment of recurrent acute pancreatitis by cutting the sphincter of Oddi, thus preventing a reflux of bile into the pancreatic duct. In this series, 5 patients were submitted to endocholedochal sphincterotomy, and it is felt that this operation can be performed safely without danger of producing cholangitis by duodenal reflux. Further, it is felt this operation is the procedure of choice if reflux of bile into the pancreas through a common biliary pancreatic passageway can be demonstrated.

FRANCIS D. MURPHY.

GASTON, E. A. Total pancreatectomy.

*New Eng. J. Med.*, 238: 345 (Mar.) 1948. This paper is a report of total pancreatectomy in a case of carcinoma of the pancreas which survived for eight days and which was intensively studied. The sixteen cases of total pancreatectomy reported in the literature are analyzed. The postoperative diabetic state, liver changes, digestion and absorption are discussed. The author gives suggestions for the care of patients after total pancreatectomy.

ANTHONY M. KASICH.

#### ULCER

BOEREMA, I. Gastroduodenal ulcer, a spastic disease. *Ann. Surg.*, 127: 413 (Mar.) 1948.

Immediately after the outbreak of World War II there was an increase in the number of peptic ulcers seen by physicians in Holland. The early rise "may be attributed to psychic factors such as fear, sorrow and rage, since at that time there was no appreciable change in food supplies." In the Groningen hospitals 145 patients were operated on because of ulcer in 1939. This number had risen to 347 by 1943.

The incidence of volvulus, anal fissure and non-bacterial diarrhea was also increased during German occupation of Holland. Since these conditions are associated with increased peristalsis or spasticity of the intestinal tract, Boerema suggests that this statistical finding is evidence in favor of the theory of von Bergmann that ulcer is a spastic (neurogenic) disease.

It was noted that the incidence of acute appendicitis fell during the occupation. This, the author assumes, resulted from better emptying of the appendix in the presence of increased peristalsis. The degree of acidity of the stomach decreased, rather than increased, during the occupation. Thus, spasm is emphasized rather than acidity as the important factor in the mechanism of ulcer formation.

LEMUEL C. McGEE.

LAKE, N. C. The aftermath of gastrectomy.

Brit. Med. J., 4545: 285 (Feb.) 1948.

A follow-up study was made of 615 patients subjected to partial gastrectomy. Peptic ulcer had been present in 488, gastric carcinoma in 87, jejunal ulcer in 35, sarcoma in 3 and linitis plastica in 2. A modified Polya operation, including the removal of about two-thirds of the stomach and the establishment of an end-to-side anastomosis with a restricted and valvular orifice, was found to give good results in the vast majority of cases.

There was not a single instance of macrocytic anemia. With the so-called complete Polya anastomosis, there was almost always achlorhydria; with the restricted valvular orifice, a small amount of acid was present in a few cases. There were 6 instances of jejunal ulceration, an incidence of approximately 1 per cent. Necrosis of the omentum occurred as a complication in 6 patients, all of whom recovered. The series includes 20 instances of the "dumping" syndrome. Attention also is directed to a syndrome of nausea on awakening in the morning, usually disappearing when the patient assumes an erect position or takes food or drink. The author concludes that gastrectomy is probably the most permanently satisfactory method of dealing

with chronic peptic ulceration at the present time.

JOSEPH B. KIRSNER.

WULFF, H. B. Vagotomy for peptic ulcer. Theoretical background and clinical results. *Acta Chir. Scand.*, 96: 265 (Dec.) 1947.

Twenty-two cases of chronic gastro-duodenal ulcer were subjected to transpleural supradiaphragmatic vagotomy. All cases were of long standing. Several had undergone partial gastrectomy. The operation of vagotomy is comparatively simple, and the technique employed was a modification of the one described by Dragstedt. Histamine and insulin tests of gastric secretion were performed before and after operation to determine if the denervation was complete. Histamine acts directly on the gastric mucosa. There was a slight reduction in the secretion postoperatively, which is attributed to the removal of the cephalic phase of gastric secretion. The action of insulin is mediated via the vagus nerve, and a marked drop in secretion is expected after vagotomy. This was found to be the case. Nearly all of the patients felt clinically improved by the operation. In two cases there was the temporary disturbance of increased intestinal motility. Two other cases required gastro-enterostomy 6 weeks following vagotomy, because of gastric retention. These individuals had shown pyloric stenosis before vagotomy. Prolonged observation of at least 10 years is required before the profession can be certain that the operation of vagotomy is the answer to the surgical treatment of peptic ulcer.

PHILIP LEVITSKY.

OBERHELMAN, H. A., JR. AND DRAGSTEDT, L. R. Effect of vagotomy on gastric secretory response to histamine. *Proc. Soc. Exp. Biol. Med.*, 87: 336 (Mar.) 1948.

Isolated innervated total stomach pouches in dogs were prepared according to the method of Dragstedt and Ellis. After control collection of gastric secretion, 1 mg. of histamine phosphate was given subcutaneously and the gastric juice secreted in the following 75 minutes was examined for

volume, and free and total acidity. Then a transthoracic section of the vagus section was performed, and confirmed by negative response to insulin hypoglycemia. Following complete division of the vagus nerves, the volume of gastric juice secreted in response to histamine decreased by 50, 67, and 44 per cent respectively; the total hydrochloric acid output in response to histamine was diminished by 62, 77, and 60 per cent respectively. In 2 of the animals, the effect of atropine on the secretion produced by histamine was determined both before and after section of the vagi. Two mg. of atropine sulphate was given subcutaneously, and 30 minutes later a second subcutaneous injection of one mg. of histamine phosphate. Following atropine, the volume of gastric juice was reduced in the one case by 88, and in the other by 82 per cent. The total acid output decreased 93 and 88 per cent respectively. Following vagotomy, atropine exerted as great an inhibition on the gastric secretory response to histamine as before.

Studies were also conducted on 2 groups of patients, 15 peptic ulcers treated by transthoracic section of the vagus nerves at Billings Hospital and 18 ulcer patients with transabdominal gastric vagotomy at the Illinois State Penitentiary. Gastric vagotomy in man also markedly reduced the gastric secretory response to a standard dose of histamine.

#### H. NECHELES.

**STEIN, I. F., JR. AND MEYER, K.** Studies on vagotomy in the treatment of peptic ulcer. *Surg. Gyn. Obs.*, 86: 473 (Apr.) 1948.

This paper is concerned primarily with the insulin test of vagus action on the stomach in 27 patients with peptic ulcer. It was found that insulin provokes increased gastric motility and acidity by hypoglycemic stimulation of the vagal center, and the reaction is abolished by complete vagotomy.

FRANCIS D. MURPHY.

#### PROCTOLOGY

**SWINTON, N. W.** Diagnosis and treatment of mucosal polyps of the rectum and colon, with early malignant change. *Am. J. Surg.*, 75: 369 (Feb.) 1948.

Polyps of the terminal colon are true tumors and are clinically considered premalignant lesions. Over 50 per cent of these benign polyps are within reach of the 10-inch sigmoidoscope but the radiologic detection of small tumors beyond this point is unsatisfactory. Maximum exposure of these premalignant lesions requires routine sigmoidoscopy in all patients over 35 years of age.

Here 22 patients are reported with mucosal polyps of the rectum and colon having early malignant change, treated by local excision, and followed for varying intervals of time up to 7 years with no recurrences. For carcinoma of the colon and rectum radical surgery is strongly advocated.

Palpation of these tumors are of great value in detecting malignancy. The soft, pulpy, non-indurated, freely movable polyp will rarely be carcinomatous. Induration, fixation and ulceration to the examining finger, however, are almost always pathognomonic of malignancy. Visualization of these tumors is less important than palpation of histologic study. The typical ulcer of malignant disease with firm, rolled edges is diagnostic. The final diagnosis in a polyp depends on histologic examination from all sections of the tumor.

MICHAEL W. SHUTKIN.

**BINKLEY, G. E. AND SUNDERLAND, D. A.** Diagnosis and treatment of papillary adenomas of the rectum. *Am. J. Surg.*, 75: 365 (Feb.) 1948.

The most common tumors found in the rectum are those which arise from the mucosal glands and are classified as adenomatous tumors. Histologically benign adenomas are often termed polyps, while the malignant variety are known as malignant polyps or rectal cancer. The benign group are classified into the following types: (1) areas of hyperplasia, (2) adenomas (the most common), and (3) papillary adenomas which may reveal atypical changes with or without malignant transformation.

Factors to be considered in estimating malignant probabilities are induration, ulceration, color, and bleeding or oozing following moderate trauma to the polyp. The objective of treatment in all cases is

complete eradication of the tumor with a minimum amount of morbidity and rectal deformity. Removal may be performed by an electric snare with or without fulguration of the base. In certain cases local surgical removal by dissection and suture is the method of choice. Radiation therapy is reserved unless the above methods fail to eradicate the disease completely. It consists of external applications of high voltage roentgen rays, surface applications of radium and intestinal implantations of gold-filtered radon seeds. Radical surgical excision of the rectum constitutes the third step of treatment and is reserved for failures after the above, less radical, methods and for fully developed carcinoma. Post-treatment observations are essential because of the marked tendency to recurrence and malignant degeneration.

MICHAEL W. SHUTKIN.

TURELL, R. The surgical treatment of chronic anal fissure. *Surg. Gyn. Obs.*, 86: 434 (Apr.) 1948.

A rational operative procedure for the treatment of chronic anal ulcer (fissures) based on experience obtained in civilian and military practice in the treatment of 270 patients, is described and illustrated. This operation consists of wide excision of the ulcer-bearing area, the extirpation of the involved anal crypt or crypts with the sentinel pile and polyps, and the performance of a posterior sphincterotomy. Immediate postoperative convalescence is smooth and uneventful.

FRANCIS D. MURPHY.

#### PHYSIOLOGY: MOTILITY

SWENSON, P. C. AND MANGES, W. E. Roentgen findings in functional disturbances of the gastro-intestinal tract. *Radiol.*, 50: 365 (Mar.) 1948.

The autonomic control of the digestive tract is a complicated mechanism. Experimental studies as well as certain clinical evidence show that the alimentary tube has an inherent mechanism of its own which, if allowed to function by itself, under ordinary conditions will carry on as an autonomous unit. The regulatory effect of the autonomic nervous system is called into action

when and if there is a necessity for an added control to modify and correlate this inherent mechanism. Then, and only then, does it become an important factor in the function of the alimentary tube. If we are to accept the chemical mediator theory as the most likely controlling mechanism of tone and contraction and relaxation of smooth musculature, then it is quite evident that this secondary role of the autonomic nervous system may take a prominent part in functional abnormalities of the entire tract or any portion thereof.

The authors have attempted to show how the roentgen patterns may be altered in the case of various disturbances of body functions both alimentary and extra-alimentary. The radiologist can find much of interest both organically and functionally in the mirror of the gastro-intestinal tract, which so often reflects the general health of the individual.

FRANZ J. LUST.

#### PHYSIOLOGY: ABSORPTION

HUMOIRO, F., VALDÉS, R., AND DÁVILA, M. Influence of the autonomic nervous system on the intestinal absorption of a hypertonic solution. *J. Pharmacol. Exp. Therap.*, 92: 336 (Mar.) 1948.

When 4 cc. of a 10% glucose solution is placed into a 16 cm. loop of small intestine of a cat anesthetized with nembutal, there is first an increase in volume followed by a decrease; the glucose is absorbed rapidly during the first few minutes and more slowly later. Atropine prevents the increase in volume but does not affect the absorption of glucose. Prostigmine and ergotamine increase the volume significantly; prostigmine does not affect the absorption of glucose, but ergotamine reduces it. Stimulation of the splanchnic nerve with or without the adrenals has no influence on the volume, however with the adrenal the absorption of glucose is accelerated. Section of the vagi does not change the absorption of fluid but accelerates the absorption of glucose. Stimulation of the vagi causes a greater increase in volume and also alters the glucose absorption.

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ARTHUR E. MEYER.

## MISCELLANEOUS

KIRCHNER, A. A. A gastroenterological comparison of white and colored soldiers.

Rev. Gastroenterol., 15: 218 (Mar.) 1948.

Over approximately 5 years 1,665 patients were admitted to the gastroenterological service of two military hospitals; 1,525 were white and 140 were colored soldiers. The most frequent diagnosis was peptic ulcer. Among the whites 597 (39.1%) had ulcer with 94.8 per cent duodenal and 5.2 per cent

gastric. Among the colored 66 (47.1%) had ulcer with 96.6 per cent duodenal and 3.4 per cent gastric. An analysis of the incidence of other diseases indicates that gastric ulcer, perforated peptic ulcer, psychoneurosis, gastritis, acute gastroenteritis, fissure-in-anus, infectious hepatitis, cholelithiasis, cholecystitis, cancer, undulant fever, malaria, diabetes and anomalies occur with practically identical frequency in both races.

C. WILMER WIRTS, JR.

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